The Journal of Pediatrics

VOL. 55 OCTOBER, 1959 No. 4

EXPERIMENTAL AND EPIDEMIOLOGIC BASIS FOR THE INTERPRETATION OF TUBERCULIN SENSITIVITY

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IT HAS been recognized for some time that nearly everyone who has had a tuberculous infection reacts to an intracutaneous test with the intermediate dose (0.0001 mg.) of PPD. Recent epidemiologic research indicates, however, that the converse is not true. In some geographic areas, many of the reactions to the intermediate dose, and most of the reactions to stronger doses, are not caused by tuberculous infection: they are cross-reactions, caused by natural infection with essentially nonpathogenic mycobacteria. The identity of several of these mycobacteria has been suggested in previous reports[1-5] by results of comparative testing with PPD tuberculin and with antigens prepared like PPD from other types of mycobacteria.

The present paper reports the results of a laboratory study in which we tried to reproduce in guinea pigs what we believe happens naturally to human beings. Some of the animals were infected with virulent tubercle bacilli, some with another type of mycobacterium, and some were not infected. Theoretical "populations" were then made up to contain varying proportions of each of the three groups of animals. The patterns of tuberculin sensitivity in the different populations of guinea pigs are shown to parallel in every important respect the patterns observed in different human populations, and thus to corroborate the epidemiologic evidence that infection with other mycobacteria causes a great deal of the tuberculin sensitivity found in human beings in many parts of the world.

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EXPERIMENTAL MATERIAL

Material for the present report was obtained as a by-product from a laboratory study on guinea pigs designed to investigate the virulence, and the sensitizing and immunizing properties, of the "Battey" mycobacterium. Experimental groups which were suitable for present purposes involved a total of 424 Hartley strain guinea pigs: 152 had been infected with the Battey organism; 147 with virulent

tubercle bacilli; 87 with the Battey organism, and, later, with virulent tubercle bacilli; and 38, which served as normal controls, had not been infected with either organism. Animals from the different experimental groups were housed together so that differences in environmental conditions throughout the quarters would be equalized among the groups.

The nonphotochromogenic acid-fast bacillus referred to as the Battey organism, originally isolated from patients at the Battey State Hospital, Rome, Georgia,[2] was used to infect the first group of animals. A culture of organisms (strain number 100616), obtained from Dr. Raymond Corpe at Battey Hospital, was grown on Long's medium, scraped off, dried, weighed, and diluted with normal saline to make a suspension containing 0.75 mg. moist weight of organisms per 0.1 ml. As determined by plate counts, the suspension contained 1.6×10^8 viable bacillary units per 0.1 ml. The animals were infected by intracutaneous injection of 0.1 ml.

The second group of animals was given an intraperitoneal injection of 1.0 ml. of a suspension of virulent tubercle bacilli (H37Rv) obtained from Dr. Leon Schmidt, Christ Hospital Research Institute, Cincinnati. Plate counts of the suspension gave an estimate of 5.4×10^4 viable bacillary units per 1.0 ml.

The third group was inoculated at the same time and with the same dose of Battey organisms as the first group; they were subsequently inoculated intraperitoneally with virulent tubercle bacilli.

The normal control group was not inoculated with either organism but was given, instead, a "placebo" injection with saline.

All of the animals were given intracutaneous tests with both PPD-S and PPD-B in doses of 0.0005 mg. in 0.1 ml. PPD-S is the international standard PPD mammalian tuberculin, prepared by Dr. Florence Seibert.[9] PPD-B is the antigen made from the Battey organism for our studies. It was prepared like PPD-S, under Dr. Seibert's direction, from Battey strain 100616. Details of its preparation and previous use in human populations may be found in earlier reports.[1, 3, 5]

Reactions to the skin tests were read at 48 hours by one person who carefully measured the transverse diameter of induration. Two precautions were taken to prevent bias. First, the two antigens were randomly assigned to two specified sites on the animal's body. Second, the animals were brought to the examiner in random order without regard to the group they belonged to. In this way, we could be sure that the readings were not influenced by knowledge of the infection history of any particular animal or of which antigen was responsible for any particular reaction.

EXPERIMENTAL RESULTS

Results of the tests with both antigens in three of the four groups of animals are shown as frequency histograms in Fig. 1.

For animals infected only with virulent tubercle bacilli, the reactions to the homologous antigen, PPD-S, were concentrated between 4 and 16 mm., with an average size of 10.4 mm. Only one animal had a reaction measuring less than 4 mm. and 5 had reactions larger than 16 mm. Most of the animals also reacted to PPD-B,

the heterologous antigen, but the reactions were generally smaller than to PPD-S. The average reaction to PPD-B was 6.2 mm. All but a few were less than 10 mm., and about 14 per cent were less than 4 mm.

For animals infected only with the Battey organisms, reactions to the spleens of animals sacrificed during the observation period. Reactions of the Battey infected animals to the heterologous antigen (PPD-S) tended to be quite small, measuring 3.1 mm. on the average. None was larger than 9 mm. and about 50 per cent were less than 4 mm.

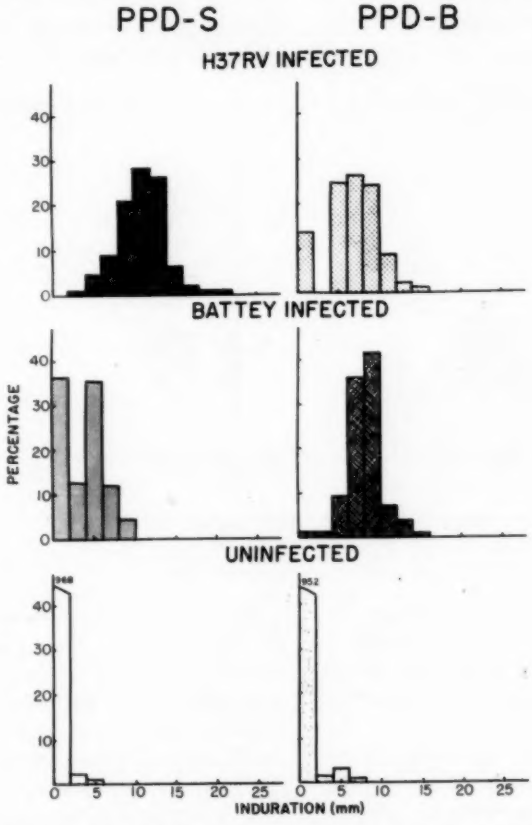

Fig. 1.—Frequency distributions of sizes of reactions to 0.0005 mg. PPD-S and PPD-B in H37Rv infected, Battey infected, and uninfected guinea pigs.

homologous antigen, PPD-B, were concentrated between 4 and 12 mm., with an average of 7.5 mm. Essentially all of the animals became sensitive to PPD-B, and Battey organisms in pure culture were recovered from

Only a very few of the uninfected animals had a measurable reaction to either antigen. In order to show clearly that small reactions were, however, occasionally found, the distribution given in the figure is for

tests at five different times—or a total of 190 tests—on the 38 animals in the uninfected group. These small reactions, which may represent observational errors, or trauma produced by the intracutaneous injection, or other unknown causes, are invariably encountered when an effort is made to measure the reactions as precisely as possible and to do it "blind," that is, without knowledge of whether or not the animal has had an infection. In our experience, it is not possible to distinguish small reactions in the uninfected from those of the same size in infected animals.

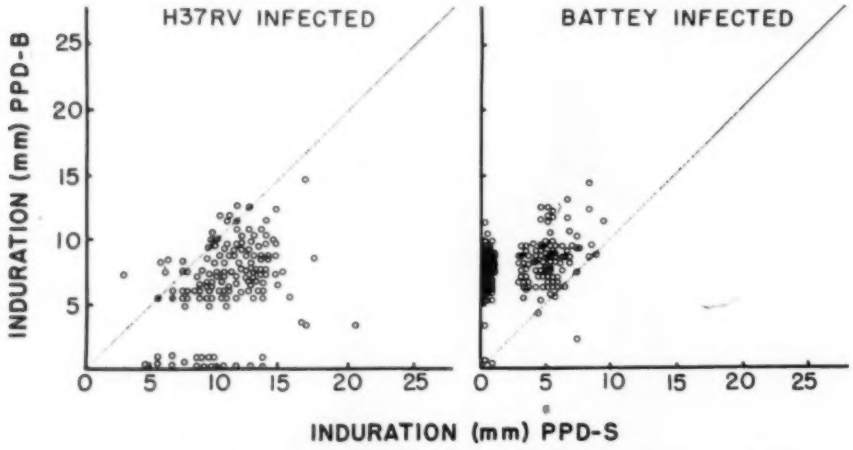

Fig. 2.—Correlations of sizes of reactions to 0.0005 mg. PPD-S and PPD-B in H37Rv infected and Battey infected guinea pigs.

Correlations of the sizes of reactions to the homologous and heterologous antigens in animals infected only with virulent tubercle bacilli or with the Battey organism are shown in Fig. 2. With few exceptions, the reaction to the homologous antigen was larger than to the heterologous antigen; this was true for animals with virulent infection as well as for those with Battey infection. These results suggest that, if the larger reaction of the pair were taken to indicate the identity of the infecting organism, the source of infection would be diagnosed correctly in 90 per cent of the 299 animals. The diagnosis would be wrong in 4 per cent where the heterologous antigen produced the larger reaction, and doubtful in the remaining 6 per cent where reactions to both antigens were the same size.

Fig. 3 shows the correlation of sizes of reactions for the group of 87 animals infected with the Battey organism and then superinfected with virulent tubercle bacilli. Reactions to PPD-B were essentially the same size as in the group infected only with the Battey organism: practically all of the animals reacted to PPD-B, the average size of the reactions being 6.9 mm. Reactions to PPD-S were essentially the same as in the animals infected only with H37Rv. None had a reaction of less than 5 mm. and the average for the group was 11.2 mm. In fact, the reactions to both

antigens were very much like those of animals infected only with H37Rv, with one exception: whereas almost all of the doubly infected animals reacted to both antigens, some 14 per cent of the singly (H37Rv) infected animals reacted only to PPD-S and not to PPD-B.

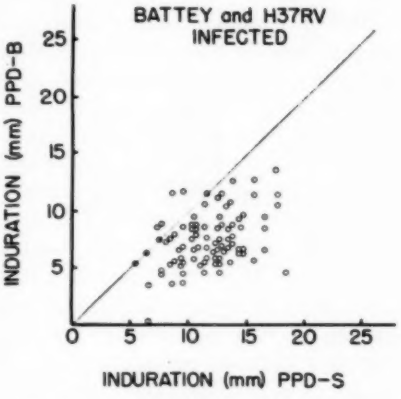

Fig. 3.—Correlation of sizes of reactions to 0.0005 mg. PPD-S and PPD-B in animals infected first with the Battey organism and then with H37Rv.

It appears from these results in guinea pigs that infection with Battey organisms does not affect the degree of sensitivity to PPD-S produced by a later virulent infection, and that a later virulent infection does not affect the sensitivity to PPD-B produced by a previous Battey infection. Thus, even if a Battey infection has preceded a tuberculous infection, it is still possible, by comparing the sizes of the reactions to PPD-S and PPD-B, to identify most of the animals that have had a virulent infection. In general, however, the converse is not true; infection with virulent organisms destroys the possibility of knowing whether or not infection with Battey organisms has also occurred. This is perhaps a fortunate circumstance, as the recognition of individuals with tuberculous infection may be far more important than identifying those among them who have also had another mycobacterial infection.

PATTERNS OF SENSITIVITY IN POPULATIONS OF GUINEA PIGS

Uninfected and Tuberculous Infected.—Frequency histograms of the sizes of reactions to PPD-S are shown in Fig. 4 for populations of guinea pigs made up to contain different proportions of uninfected and tuberculous (H37Rv) infected animals. Starting at the top of the figure, the first histogram is for a population composed of 80 per cent tuberculous infected and 20 per cent uninfected; the next histogram is for 40 per cent infected and 60 per cent uninfected; and so on, down to the last histogram, which is for 5 per cent infected and 95 per cent uninfected. The darkly shaded portion of each histogram represents the reactions of the infected animals; the lightly shaded portion represents the uninfected.

The pattern for most of the histograms is clearly bimodal, with one modal group at the extreme left and the other centered at 10 to 11 mm. Such a pattern would be expected, as most of the uninfected animals had no reaction and the average reaction of the infected animals was 10.4 mm. (cf. Fig. 1). In the interval between the two modes, the right tail of the uninfected group and the left tail of the infected group overlap; and in this range of overlap both uninfected and infected animals had reactions of equal size.

In using the tuberculin test to distinguish between the infected and the uninfected, the usual procedure is to set the criterion for separation at a certain size and to classify all subjects with larger reactions as infected and those with smaller reactions as uninfected. The problem of selecting the criterion which will provide the most efficient separation of the two groups is illustrated by these experimental results. Because of the overlapping of the two groups, a perfect separation would not be possible; wherever the criterion were set, some of the infected would be misclassified as uninfected, or some of the uninfected would be misclassified as infected, or both. The point at which the most efficient separation—the separation resulting in the fewest misclassifications—can be made varies according to the proportion of infected in the population. In this particular material, for example, when the proportion of infected is high, separation between 3 and 4 mm. would result in relatively few misclassifications because most of the reactions in the range of overlap belong to the infected group. When the proportion of infected is low, the best separation would be between 5 and 6 mm. as most of the reactions in the range of overlap belong to the uninfected group. For intermediate proportions, however, when more or less equal numbers from both groups fall into the range of overlap, it is more difficult to determine where to make the separation; the decision would have to depend on whether it is more important to classify most of the infected correctly and misclassify some of the uninfected, or vice versa.

These experimental results illustrate that when a population is composed only of tuberculous infected and uninfected subjects, the tuberculin test can separate the two groups with a high degree of precision, even though the separation will not be perfect.

Uninfected, Tuberculous Infected, and Battey Infected.—The histograms in Fig. 5 illustrate the variations in the patterns of reactions to PPD-S, and some of the problems that arise when animals infected with an organism that produces tuberculin cross-reactions are included in a population of uninfected and tuberculous infected animals. The generally small (cross) reactions of Battey infected animals more or less fill in the interval of low frequency between the uninfected and the tuberculous infected. In fact, reactions of the Battey infected group center in the range where the other two groups could have been most efficiently separated.

The degree to which Battey infected animals dominate the pattern of sensitivity for the population depends on the relative proportions of Battey infected and tuberculous infected. When the proportion of tuberculous infected is high and of Battey infected is low, as in the top histogram, the pattern is dominated by the tuberculous infected group with a peak at 10 to 11 mm. But when the proportion of tuberculous infected is low, the Battey infected group gains in prominence with increasing proportions, and the peak is shifted to the center of the cross-reacting group at 4 to 5 mm.

Identification of the tuberculous infected in populations resembling these

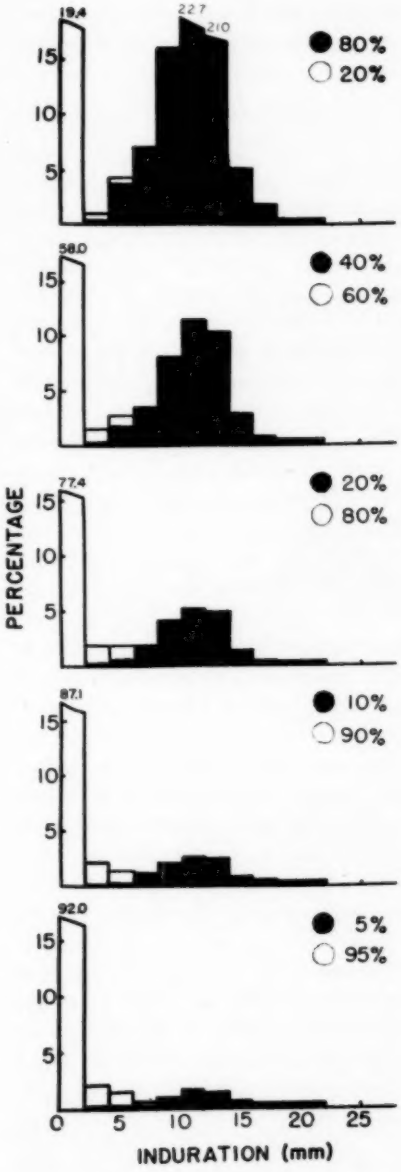

Fig. 4.—Frequency distributions of sizes of reactions to 0.0005 mg. PPD-S in "populations" of guinea pigs containing varying proportions of H37Rv infected (dark shading) and uninfected (light shading).

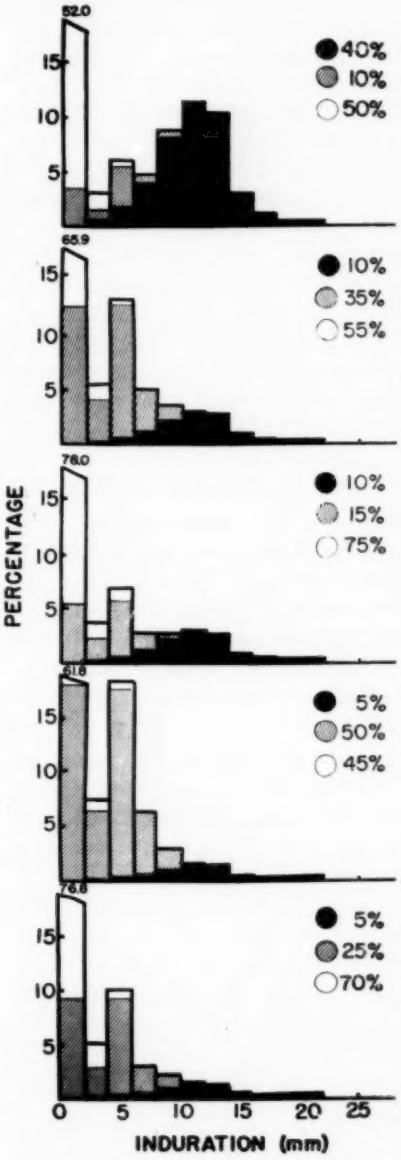

Fig. 5.—Frequency distributions of sizes of reactions to 0.0005 mg. PPD-S in "populations" of guinea pigs containing varying proportions of H37Rv infected (dark shading), Battey infected (striped shading), and uninfected (light shading).

obviously can not be done very satisfactorily with the tuberculin test alone. If, for example, the criterion of 6 mm. were applied to the results obtained for a population like the one containing 5 per cent tuberculous infected and 50 per cent Battey infected, 12.5 per cent of the total population would be classified as positive but only one-third of the "positives" would be actually tuberculous infected. Within the range where cross-reactions and reactions resulting from tuberculous infection are of the same size, it is clearly impossible to identify the tuberculous infected on the basis of the size of the reaction in the individual. Since, however, the cross-reactions are generally smaller that the true tuberculous reactions, the proportion of cross-reactions steadily decreases with increasing size of reaction: the larger the reaction, the greater the likelihood that it represents a tuberculous infection.

From these experimental results it is evident that many different patterns of tuberculin sensitivity are possible when a population contains Battey infected in addition to tuberculous infected and uninfected. The crux of the matter is that infection with the Battey organism—or any other organism that causes tuberculin cross-reactions—creates serious problems in using the tuberculin test to identify the tuberculous infected. Moreover, the error of misclassification may be very high. About the only generalization that can be made is that a large proportion of the smaller "positive" reactions may be cross-reactions; but with increasing size of the reaction, an increasing proportion represents true tuberculous infection.

OBSERVED PATTERNS IN HUMAN POPULATIONS

In recent years we have collected considerable material on the patterns of tuberculin sensitivity in groups of tuberculous patients and general population groups both in this country and abroad.[3, 6, 7, 10, 11] The material was obtained under conditions designed to produce a high degree of uniformity in the techniques and procedures used in testing the different groups. Only two carefully standardized tuberculin products were used: PPD-S for most of the work in this country, and the Danish PPD (RT 19-21) for most of the work abroad. In some studies, both antigens were used simultaneously. In addition, PPD antigens prepared from several different types of mycobacteria were also used for testing some of the patients and general population groups. The testing and reading of reactions were done by a small number of persons who had undergone a period of several months' training before being sent out into the field. The reactions were read by measuring, as precisely as possible, the diameter of induration, with no attempt on the part of the reader to classify any reaction as positive or negative.

Patients With Clinical Disease.—Within the last 2 years, adult patients in eight tuberculosis hospitals have been tested with both PPD-S and PPD-B simultaneously. Four of the hospitals are located in Florida, one in Georgia, one in Illinois, and two in

Minnesota. According to the bacteriologic reports from the hospital laboratories, only organisms identified as typical virulent tubercle bacilli were recovered from 1,434 of the patients we tested, and only organisms identified as Battey-type mycobacteria were recovered from 84. Results of skin testing these 1,518 patients are given in Fig. 6.

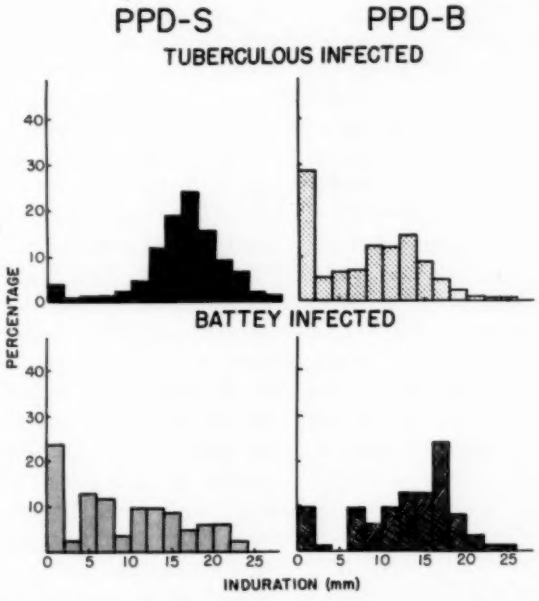

Fig. 6.—Frequency distributions of sizes of reactions to 0.0001 mg. PPD-S and PPD-B in hospitalized patients infected with typical tubercle bacilli or Battey mycobacteria.

The histograms show the sizes of reactions to 5 TU of PPD-S, and to an equivalent dose (0.0001 mg.) of Battey PPD (PPD-B), separately for patients with typical tubercle bacilli (upper section) and for patients with Battey type organisms (lower section). The sensitivity patterns for the two groups of patients are reminiscent of those for the guinea pigs infected experimentally with virulent tubercle bacilli or the Battey organism (see Fig. 1). For patients with typical tuberculous disease, the reactions to PPD-S (the homologous antigen) averaged 15.5 mm. in size, with 93 per cent of the reactions measuring between 6 and 25 mm. Only 5 per cent had reactions of less than 6 mm. The reactions to PPD-B (the heterologous antigen) were generally smaller; the average was 7.5 mm., with 39 per cent less than 6 mm. For patients with disease attributed to the Battey organism, PPD-B caused generally larger reactions than PPD-S. Almost all of these Battey infected patients reacted to the homologous antigen; and about 75 per cent of them also had some reaction to PPD-S.

Correlations of the reactions to PPD-S and PPD-B for the two groups

of patients are shown in Tables I and II. The reaction to the homologous antigen was larger than to the heterologous antigen in 90 per cent of the 1,434 patients with virulent tuberculous infection and in 68 per cent of the 84 patients with Battey infection. It is perhaps surprising that the skin test results correspond as closely as they do with the clinical diagnoses made in these patients, as some of them probably had been previously infected (and sensitized) by an organism other than the one isolated during the current illness, and little is known about the effect on tuberculin sensitivity in human beings of multiple infections with different kinds of organisms. Moreover, the classification of atypical mycobacteria is still very tentative.

General Population Groups.—The patterns of sensitivity found in general population groups show enormous variations from one geographic area to another, largely because of wide differences in the prevalence of small reactions. When the proportion of small reactions in a population is low, the pattern of sensitivity is generally bimodal; but with an increasing proportion of small reactions, the interval between the two modal groups is filled in. Fig. 7 illustrates the broad range in patterns of naturally acquired sensitivity to the intradermal 5 TU test observed in school children in different parts of the world.[10, 11] Some of the histograms are similar to those shown in Fig. 4, some resemble those in Fig. 5. The observed patterns of reactions for children in Mexico and Denmark, for example, basically resemble the patterns for experimental populations of guinea pigs which contain only tuberculous infected and uninfected. Both histograms show a clear bimodal pattern, but, as would be expected from what is known about tuberculosis in the two countries, many more of the Mexican than the Danish children appear to have had a tuberculous infection. In contrast, the patterns for children in North Carolina and Sudan resemble patterns for guinea pig populations with high proportions of animals with cross-reactions and varying proportions of tuberculous infected.

The analogy between epidemiologic and experimental results can be carried a step further with material available for U. S. Navy recruits, men between 17 and 21 years of age, who were recently tested simultaneously with both PPD-S and PPD-B. Reactions to PPD-B, as reported previously,[3] showed enormous variations in prevalence in recruits from different parts of the country—ranging from less than 20 per cent in the northwest to about 70 per cent in the southeast. Reactions to PPD-S, on the other hand, were rarely over 10 per cent in any part of the country, and variations in the proportion of small reactions paralleled the prevalence of sensitivity to PPD-B. Fig. 8* gives a simple visual analysis of the results of comparative tests with PPD-S and PPD-B for recruits from three regions of the country: northwest, northcentral, and southeast. The histograms show the distributions of reactions to 5 TU of PPD-S; and for all reactions of 6 or more mm., the relative size of the reaction to a corresponding dose (0.0001 mg.) of PPD-B is indicated by the

*Note the larger vertical scale than in the previous figures.

TABLE I. CORRELATION OF SIZES OF REACTIONS TO 0.0001 MG. PPD-S AND PPD-B IN PATIENTS WITH POSITIVE CULTURES FOR *M. tuberculosis*

Induration (mm.) to PPD-B	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total
26																												-
25																												-
24																					1							1
23																												-
22																1												1
21																					1		2		2			5
20																				3	1							4
19															1		2		2		1		1		1		1	8
18														1	1		1	1	4	6	2	3	2	1	1	2		25
17														2	1	1	2	2	6	4	2	1	3		1			30
16													1		3	3	1	6	8	5	3	1	2	3			1	37
15												1		2		6	5	2	9	6	6	3	4	3	2		1	50
14									1			1	1	1	10	5	13	8	7	7	6	4	5		1	1		71
13										2	1	3	5	2	8	5	11	17	5	8	8	4	5	5	1	1	5	96
12	2										1		5	7	12	8	18	19	12	6	5	4	1		1	2	1	104
11	2								1			2	3	8	7	11	9	12	7	7	7	3	7	4				90
10						1			1	2		1	9	6	8	10	4	9	8	6	4	3	5	4	1		1	83
9											2	1	7	7	19	6	15	4	11	3	13	6	4	1	1		1	101
8	4			1	1				1		1		1	4	10	6	12	8	13	3	1	1	3	3		1		74
7								1		1		1	5	3	5	8	7	8	2	2	3		1	4				51
6						1			1	1	2		5	3	3	4	3	7	3	2	5		2	1			2	45
5											3		2	4	4	2	6	4	4			1		3				33
4	2								1	1	4	2	1	6	8	5	10	10	1	4	4		1	1				61
3	2			1		1	2	1	1	3		4	4	3	5	3	4	4	4	5	3	1	2				1	54
2	1					1			3			1	2		3		1	3	2	1		1						19
1																												-
0	42		4	3	6	3	4	11	6	7	15	21	24	32	29	32	34	45	28	11	14	5	7	3	2		3	391
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total

Induration (mm.) to PPD-S

TABLE II. CORRELATION OF SIZES OF REACTIONS TO 0.0001 MG. PPD-S AND PPD-B IN PATIENTS WITH POSITIVE CULTURES FOR BATTEY-TYPE MYCOBACTERIA

Induration (mm.) to PPD-B	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total
26																												-
25																												-
24									1																			1
23																							1					1
22																												-
21																								1				1
20							1												1									2
19	1				1														1									3
18	1											1	1								1							4
17						1	1	1			1	1	1	2	1	1					1							11
16					2	1							1	1	1		1	1		1								9
15											1		1		1													3
14	1				1		2	2								1					1							8
13	4							1	1							1				1								9
12	1										1																	2
11					1												1											2
10					2			1	1		1					1												6
9	2				1																							3
8	1										1																	2
7	2						1											1			1							5
6	2										1																	3
5																												-
4																												-
3				1																								1
2																												-
1																												-
0	4		1		1									1							1							8
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total

Induration (mm.) to PPD-S

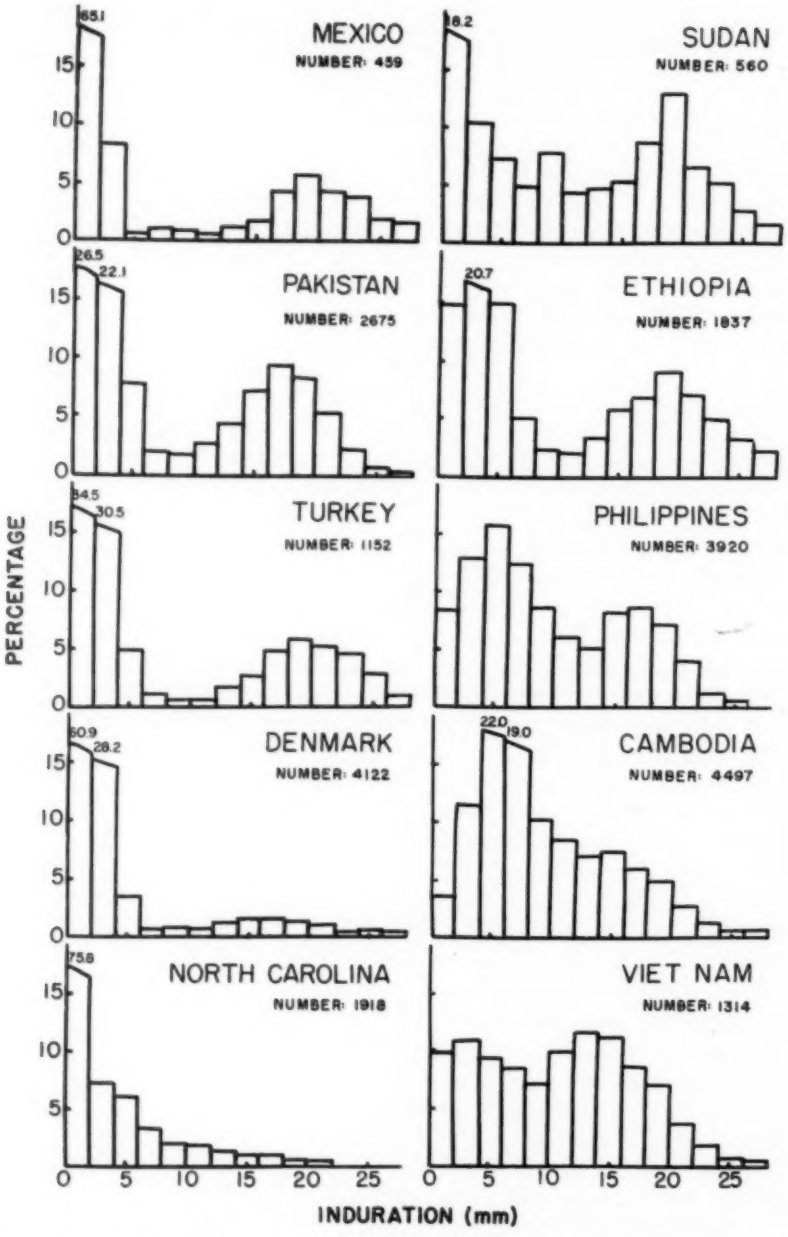

Fig. 7.—Frequency distributions of sizes of reactions to 0.0001 mg. PPD tuberculin in school-children in various parts of the world.

shading. The dark shading in each column represents the proportion of recruits whose reactions to PPD-S were larger than to PPD-B, and the striped shading represents the proportion whose reactions to PPD-B were equal to or larger than to PPD-S. (Reactions to PPD-S measuring less than 6 mm. are not similarly analyzed, because the relative sizes of reactions to PPD-S and PPD-B have little meaning in that size range where a good many of the reactions represent the uninfected portion of the population.)

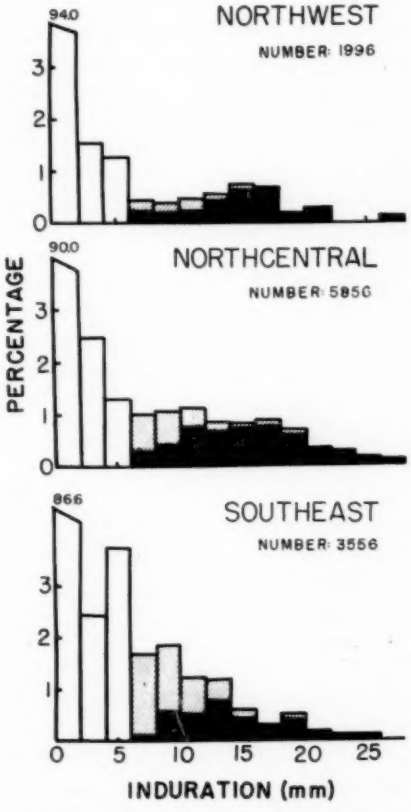

Fig. 8.—Frequency distributions of sizes of reactions to 0.0001 mg. PPD-S, and relative size of reactions to 0.0001 mg. PPD-B, in Navy recruits from three different regions of the United States.

The dark shading is for persons whose reactions to PPD-S were larger than to PPD-B; the striped shading is for those whose reactions to PPD-S were the same size or smaller than to PPD-B; and the light shading is for those with reactions of less than 6 mm. to PPD-S, regardless of the size of reaction to PPD-B.

These histograms illustrate how an increasing proportion of small reactions—many of them cross-reactions, judging from the comparative reaction to PPD-B—distorts the pattern of the distribution, and creates a serious practical problem in trying to identify the tuberculous infected by testing with PPD-S. In the northwestern region of the United States, for example, the prevalence of cross-reactions appears to be relatively low; and most of the presumably tuberculous infected can be identified fairly accurately by setting the criterion for separation at 6 mm. But with the greater prevalence of cross-reactions in the northcentral region, and the very high prevalence in the southeast, identification of the tuberculous infected becomes increasingly uncertain. A considerable proportion of the reactions of 6 to 12 mm. in the northcentral area, and a much higher proportion in the southeast, must be interpreted as cross-reactions. However, as was shown for the guinea pig populations (see Fig. 5), the larger the size of the reaction to PPD-S, the greater the likelihood that it represents tuberculous infection and not cross-sensitization by some other type of infection.

A similar analysis is shown in Fig. 9 for comparative test results in a group of adults in Minnesota and the entire population of a small community in India.[3, 4] Tests were given simultaneously with the 5 TU dose of PPD and approximately equivalent

doses of PPD antigens prepared from several different types of acid-fast organisms: *Myco. avium*, the "Cuttino" organism isolated from a patient in North Carolina, and two chromogenic mycobacteria isolated from sputum in

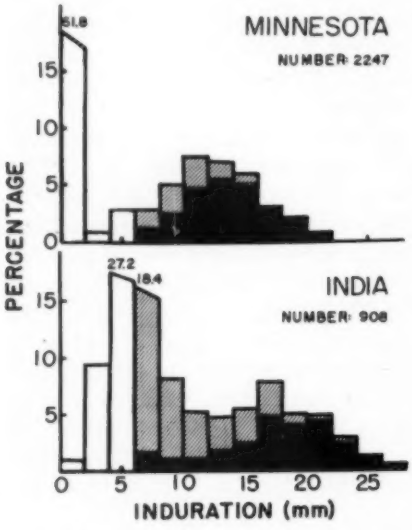

Fig. 9.—Frequency distributions of sizes of reactions to 0.0001 mg. PPD tuberculin, and relative size of reactions to equivalent doses of other mycobacterial PPD antigens, in general population groups in Minnesota (adults) and India (all ages).

The shading is the same as in Fig. 8.

India. These products are antigenically very similar to PPD-B.[3, 12] The distributions of reactions which are darkly shaded, and interpreted as representing virulent tuberculous infection, are strikingly alike in Figs. 8 and 9, but the proportion of cross reactions varies widely from one geographic area to another.

Comparative testing with PPD-S and other mycobacterial antigens seems to make it possible to identify the group of persons who presumably have not had a tuberculous infection but have been sensitized to tuberculin by infection with other mycobacteria. Whether the Battey organism is the chief culprit, or only one of a closely related group, is still uncertain; but it is evident that testing with the Battey and related antigens can be very useful for distinguishing between specific tuberculous reactions and tuberculin cross-reactions.

DISCUSSION

Striking parallels may be drawn between mycobacterial infections and systemic fungus infections, and the skin sensitivity they produce. Histoplasma, for example, is known to infect large numbers of persons; to sensitize them to the corresponding skin test antigen, histoplasmin; and to cause clinical disease in relatively few, except possibly in the very young. The same is true of Coccidioides. And because of the close antigenic relation between the two fungi, cross-reactions occur with both histoplasmin and coccidioidin.[8] For practical purposes, skin tests can be given simultaneously with both antigens; the larger reaction is interpreted as indicating the source of infection, while the smaller reaction is considered to be a cross-reaction. The geographic area in which the person has lived may also be helpful in corroborating the skin test results, as both fungi have fairly well defined, and different, geographic distributions.

Similarly, the virulent tubercle bacillus, *Myco. tuberculosis*, and other mycobacteria, including those classified at the present time as nonphotochromogens (Battey type), are so closely related antigenically that cross-reactions occur with the PPD antigens prepared from them. The Battey

organism, like Histoplasma, apparently infects and sensitizes a great many persons, and only occasionally causes clinical disease. Moreover, its distribution and prevalence, though still poorly defined, seem to be closely related to geographic factors. Tuberculosis, on the other hand, is related to contact with human and bovine sources of infection and is not limited by geographic factors.

It has been recognized for many years that infection with the bovine type of tubercle bacillus and with BCG causes tuberculin sensitivity which is indistinguishable from that caused by the human type of tubercle bacillus. Other organisms, such as the avian tubercle bacillus and *Myco. balnei*, have also been found to produce cross-reactions to mammalian tuberculin; but so far as is known these infections are probably rare in human populations. Our immediate concern, however, is not with organisms that may produce an occasional tuberculin cross-reaction; rather, it is with the other mycobacteria, such as the Battey organism, that apparently infect and sensitize vast numbers of persons in many parts of the world. The tuberculin cross-reactions resulting from these infections cause serious difficulties in identifying persons with virulent tuberculous infection, as is already well known in countries where a great many cross-reactions have been produced by BCG vaccination. Fortunately, in countries like our own, where BCG has been used sparingly, we have only the problem of naturally occurring tuberculin cross-reactions to contend with. But the significance of these cross-reactions may be expected to increase rather than decrease as our tuberculosis infection rate continues to fall. Even now, in many parts of the country, and especially in the younger age groups, infections with virulent tubercle bacilli already are a great deal less frequent than infections with cross-reacting mycobacteria.

The present results show that both in experimentally infected animals and in patients in tuberculosis hospitals, comparative tests with standard PPD-S and an appropriate dose of another mycobacterial antigen, in this case PPD-B, can distinguish most of the tuberculous infected from those infected with mycobacteria classified as the Battey type. In applying these results to healthy populations, where the cause of sensitivity can only be inferred, the comparative test technique offers promise of a way to separate persons with positive reactions into those who have had a tuberculous infection and those who have tuberculin cross-reactions caused by other kinds of mycobacterial infection. While our attention, at the moment, is focused on the problem of identifying the tuberculous infected, it may well be that as we learn more about these other infections it will become important to distinguish among them, too.

SUMMARY

Epidemiologic evidence that nontuberculous infections cause many of the positive tuberculin reactions observed in human beings is corroborated by results of experimental studies of guinea pigs reported in the present paper. Some of the animals were infected with virulent tubercle bacilli, some with the nonphotochromogenic mycobacterium of the "Battey" type, and some were not infected. Intracutaneous tests with standard mammalian tuberculin (PPD-S) and the

PPD antigen prepared from the Battey organism (PPD-B) showed that although cross-reactions occur with both types of infection, the homologous antigen usually produced a larger reaction than the heterologous antigen. Frequency histograms of the sizes of reactions to PPD-S for theoretical populations containing various proportions of tuberculous infected, Battey infected, and uninfected guinea pigs, revealed patterns of sensitivity similar to those observed in human populations.

Parallel studies of patients in tuberculosis hospitals from whom only typical tubercle bacilli or Battey-type organisms had been recovered gave results like those found in the guinea pigs.

Studies of healthy U.S. Navy recruits from different parts of the country, and of general population groups in this country and abroad, indicate that cross-reactions to tuberculin are highly prevalent in some geographic areas and much less prevalent in others; moreover, the frequency of cross-reactions varies with the prevalence of sensitivity to PPD-B. Whether the organism chiefly responsible for these cross-reactions is the Battey organism, or some other related organism (or organisms), is still undetermined. It is clear, however, that when the frequency of tuberculin cross-reactions is high and of specific tuberculous reactions is low, few of the tuberculous infected can be identified by the size of the tubercuiin reaction alone. Simultaneous testing with PPD-S and other PPD antigens can then be expected to help determine the source of the tuberculin sensitivity, just as simultaneous testing with histoplasmin and coccidioidin helps to distinguish between the two fungus infections.

The authors take this opportunity to acknowledge the efforts of numerous people who have contributed to the collection of material presented in this paper. We are indebted to the many members of the Tuberculosis Program in Chamblee, Georgia, and in Washington, as well as to the staff of the WHO Tuberculosis Research Office, Copenhagen, Denmark, and the national and local health authorities of many countries whose cooperation has been invaluable. Particular mention should be made of Dr. Benjamin L. Brock of the Central Florida Tuberculosis Hospital; Dr. Sumner S. Cohen of the Glen Lake Sanatorium, Oak Terrace, Minnesota; Dr. Raymond F. Corpe of the Battey State Hospital, Georgia; Dr. George H. Hames of the Southeast Florida Tuberculosis Hospital; Dr. T. William Lester, Jr., of the Suburban Cook County Hospital, Hinsdale, Illinois; Dr. Albert G. Lewis of the Southwest Florida Tuberculosis Hospital; Dr. Lawrence C. Manni of the W. T. Edwards Tuberculosis Hospital, Tallahassee, Florida; Dr. George C. Roth of Ancker Hospital, St. Paul, Minnesota; Dr. Tracy E. Barber of Austin, Minnesota; and Dr. John F. Chace, Director of Tuberculosis Control, Bureau of Medicine and Surgery, Navy Department. The material from North Carolina was obtained from an epidemiologic study of tuberculosis being carried out in Pamlico County under the joint auspices of the state and local health departments, the North Carolina affiliated state tuberculosis associations, and the North Carolina Sanatorium System.

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THE BLOOD VOLUME OF INFANTS

II. The Premature Infant During the First Year of Life

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THE purpose of this investigation was to study the total blood, plasma, and erythrocyte volumes, and the total circulating hemoglobin mass of premature infants from birth through the first year of life.

Previous studies in this laboratory[1] demonstrated that wide variations in these volumes occur in full-term infants. It was anticipated that variations would also be encountered in premature infants. The study was designed to determine if expected deviations would be the result of changes within single infants and not simply random differences between individuals. For this reason, serial observations were made of most of the infants selected. It was felt that the assessment of iron-deficiency anemia, so common among premature infants, would be improved by volumetric studies carried out over many weeks.

MATERIALS AND METHODS

The subjects of this investigation were 51 premature infants in good condition, on whom 145 plasma volume determinations were performed. Six serial observations were made of 1 infant, 5 of 8 infants, 4 of 9, 3 of 10, 2 of another 10, and a single observation of 13 infants.

The babies were born in this hospital of healthy women. No infant was included whose mother had systemic disease, severe complications of pregnancy, or an operative delivery. Other bases for selection of the infants were physical normality and lack of hematologic, respiratory, or other systemic complication in the delivery room or nursery. The birth weights ranged from 1,200 to 2,350 grams. Five sets of fraternal twins were included, Cases 18 and 19, 22 and 23, 28 and 29, 45 and 46, and 50 and 51.

It was practically impossible to control the total environment of this large group of infants of such diverse background, except for assuring equally adequate diet, cleanliness, and care. In this we were ably assisted by the efforts of the Visiting Nurse Association. Since contact could not be maintained with all the families, serial observations (2 or more) were made on only 38 of the 51 subjects.

During the course of the investigation, an average of 2 mild upper respiratory infections were recorded for subjects followed for more than 6 months. The twin infants, 28 and 29, contracted varicella and rubella. Five

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Supported by Grant A515 (C) from the Institute of Arthritis and Metabolic Diseases of the National Institutes of Health.

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infants (1, 24, 25, 37, and 40) developed iron-deficiency anemia and it was deemed necessary to institute iron therapy. This is indicated in Table II.

Micro- and semimicro-laboratory techniques were employed to avoid producing anemia from blood loss in the subjects. A maximum of 3.5 ml. of venous blood was withdrawn for each set of determinations.

Plasma volume measurements were done by the method of Nitsche and Cohen[2] using T-1824, and with the extraction of dye in acetone-water as described by Allen.[3] Microhematocrit determinations were done in duplicate. Hemoglobin concentrations were measured by the cyanmethemoglobin method of Crosby, Munn, and Furth.[4] Serum iron concentrations were done by the method of Burch, Lowry, Bessey, and Berson,[5] and latent serum iron-binding capacities by the method of Rath and Finch.[6]

Blood volume was calculated from plasma volume, using factors for plasma trapped in the red cell column of the hematocrit tube[7] and for body/venous hematocrit ratio.[8] Erythrocyte volume was taken as the difference between total blood and plasma volumes.

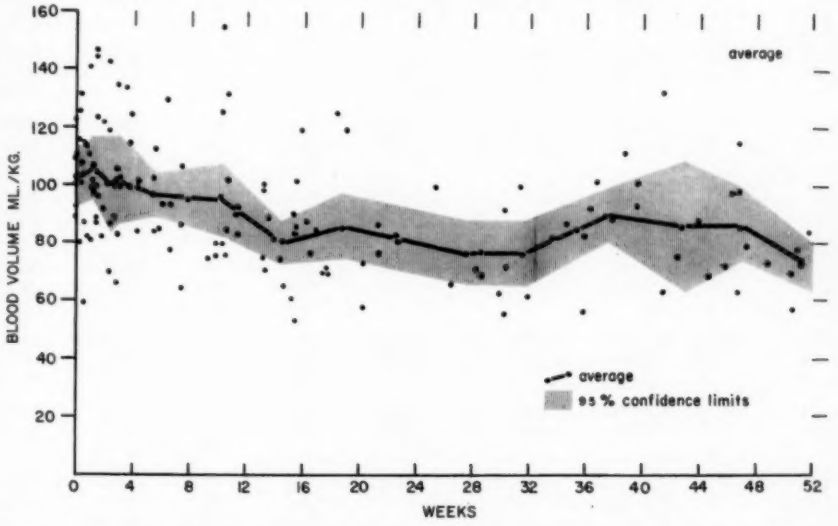

Fig. 1.—Individual values of total blood volume based on kilograms of body weight are plotted against age in weeks. The heavy line denotes the mean values from birth through 52 weeks. The shaded area represents the 95 per cent confidence intervals for each period. Many points lie beyond the confidence limits, indicating the very wide deviations that occur throughout the first year of life.

RESULTS

A summary of average values with medians for intervals of age in weeks is presented in Table I. The results of 3 or more serial observations of individual infants are listed in Table II. The volumetric data are expressed in milliliters per kilogram of body weight, and data for circulating hemoglobin mass in grams per kilogram.

Blood Volume.—Fig. 1 illustrates the range of values found in all of the

TABLE I. PREMATURE INFANTS—BIRTH

	NUMBER OF TESTS	AGE AT TEST	AGE INTERVAL AT TEST	WEIGHT AT TEST (GM.)	HEMOGLOBIN (GM./100 ML.)	HEMATOCRIT (PER CENT)	PLASMA VOLUME (ML./KG.)	PLASMA VOLUME (TOTAL ML.)
Mean	17	3.4 da.	3 hr.-6 da.	1,999	17.0	50.8	59.3	117.2
Median		3.0 da.	3 hr.-6 da.	1,920	17.0	50.0	59.7	110.0
S.D.					±1.81	±6.65	±10.55	
Mean	15	1.3 wk.	1.0-1.9 wk.	1,951	15.2	45.1	66.9	130.3
Median		1.3 wk.	1.0-1.9 wk.	2,000	15.3	47.0	64.8	126.0
S.D.					±2.81	±8.95	±14.62	
Mean	8	2.3 wk.	2.0-2.9 wk.	1,883	14.6	42.8	64.1	117.7
Median		2.3 wk.	2.0-2.9 wk.	1,830	14.5	43.8	57.0	117.0
S.D.					±1.93	±5.08	±14.49	
Mean	8	3.1 wk.	3.0-3.9 wk.	2,064	11.9	35.1	72.8	146.5
Median		3.1 wk.	3.0-3.9 wk.	2,020	11.6	34.3	72.7	145.0
S.D.					±1.73	±4.10	±16.32	
Mean	17	5.7 wk.	4.0-7.6 wk.	2,629	10.3	29.1	73.4	190.0
Median		5.4 wk.	4.0-7.6 wk.	2,590	9.6	29.0	72.4	184.0
S.D.					±1.49	±4.71	±12.49	
Mean	14	10.5 wk.	8.1-11.7 wk.	3,779	9.9	28.9	72.6	269.8
Median		10.5 wk.	8.1-11.7 wk.	3,755	9.8	29.0	65.3	271.5
S.D.					±0.71	±2.21	±17.90	
Mean	14	14.6 wk.	13.0-15.9 wk.	4,586	9.9	28.7	61.1	281.1
Median		14.8 wk.	13.0-15.9 wk.	4,590	9.8	28.3	62.9	277.5
S.D.					±0.86	±1.89	±10.97	
Mean	14	18.9 wk.	16.0-22.9 wk.	5,045	9.8	30.4	64.1	326.3
Median		18.2 wk.	16.0-22.9 wk.	5,000	9.8	31.0	58.1	318.0
S.D.					±1.50	±4.45	±15.67	
Mean	5	27.6 wk.	25.0-29.9 wk.	6,512	9.5	29.1	58.3	376.6
Median		28.4 wk.	25.0-29.9 wk.	6,280	8.5	28.0	51.7	385.0
S.D.					±1.33	±2.87	±10.68	
Mean	8	31.6 wk.	30.0-34.9 wk.	6,711	8.6	29.1	58.2	387.3
Median		30.9 wk.	30.0-34.9 wk.	7,130	9.1	29.5	55.8	381.0
S.D.					±2.00	±3.55	±11.66	
Mean	9	37.4 wk.	35.0-39.9 wk.	6,738	8.5	28.1	68.9	467.3
Median		36.7 wk.	35.0-39.9 wk.	7,000	8.0	27.0	72.1	467.0
S.D.					±1.82	±4.14	±12.13	
Mean	5	42.9 wk.	40.0-44.9 wk.	7,758	9.1	31.0	64.0	494.6
Median		42.6 wk.	40.0-44.9 wk.	7,930	9.4	32.0	55.4	404.0
S.D.					±1.41	±2.61	±17.75	
Mean	7	47.0 wk.	45.0-49.9 wk.	8,049	9.0	29.2	65.1	518.3
Median		46.6 wk.	45.0-49.9 wk.	7,880	9.7	30.0	61.5	478.0
S.D.					±2.29	±4.90	±11.99	
Mean	4	51.3 wk.	50.0-52.0 wk.	9,223	8.7	28.5	55.7	512.2
Median		51.2 wk.	50.0-52.0 wk.	9,275	9.3	29.5	58.6	528.0
S.D.					±1.85	±3.35	±7.30	

infants in the study by age in weeks. The heavy line, representing the mean, lies in a shaded area denoting the 95 per cent confidence limits. Four infants were observed on the first day of life. Their average blood volume was 109 ml. per kilogram, a value almost exactly that calculated by Schulman, Smith, and Stern.[9]

Mean values are undependable owing to wide deviations about the means encountered throughout the

THROUGH FIRST YEAR OF LIFE

BLOOD VOLUME (ML./KG.)	BLOOD VOLUME (TOTAL ML.)	ERYTHROCYTE VOLUME (ML./KG.)	ERYTHROCYTE VOLUME (TOTAL ML.)	HEMOGLOBIN MASS (GM./KG.)	HEMOGLOBIN MASS (TOTAL GM.)	SERUM IRON (μG %)	LATENT IRON-BINDING CAPACITY (μG %)	HEMOGLOBIN IRON (TOTAL MG.)
102.7	203.2	43.4	86.1	17.6	34.9	95.7	14.7	118.7
102.2	206.0	44.5	82.0	18.5	34.0	100.0	0	
±17.45		±10.41		±3.79				
106.0	206.4	39.8	76.3	16.2	31.1	108.0	37.5	105.7
99.1	200.0	38.8	73.0	16.1	31.0	102.0	0	
±21.51		±11.35		±4.22				
99.6	182.3	35.5	64.5	14.5	26.6	118.1	21.9	90.4
89.7	172.5	34.5	62.0	14.8	25.0	115.5	0	
±23.17		±9.52		±3.77				
102.4	205.9	29.5	59.5	12.2	24.6	95.0	121.3	83.6
100.2	205.5	27.5	62.5	11.2	24.5	93.5	110.0	
±21.60		±6.65		±2.99				
96.9	249.7	23.5	59.8	10.1	25.6	95.1	113.3	87.0
98.2	237.0	24.3	58.0	10.2	26.0	85.0	100.0	
±16.46		±5.92		±2.53				
95.4	354.4	22.8	84.7	9.5	35.3	72.0	175.0	120.0
86.5	354.0	21.1	82.0	9.0	34.5	74.5	195.0	
±23.47		±6.26		±2.26				
80.1	369.3	19.1	88.4	7.9	36.6	55.1	184.6	124.4
82.1	358.5	19.9	86.0	8.0	34.0	55.0	200.0	
±14.44		±3.75		±1.42				
85.5	436.7	21.4	110.1	8.4	43.1	46.1	205.0	146.5
80.8	438.0	20.7	111.5	8.2	44.0	41.5	200.0	
±22.30		±5.99		±2.41				
76.5	496.2	18.3	119.6	7.2	47.6	46.6	215.0	161.8
70.8	535.0	17.4	135.0	7.4	53.0	41.0	195.0	
±12.26		±2.18		±1.07				
76.6	510.0	18.4	122.9	6.7	44.4	44.9	245.0	150.8
76.8	516.0	17.4	114.0	6.5	42.0	38.5	245.0	
±14.72		±4.05		±2.01				
90.3	606.2	20.8	138.7	7.7	51.3	35.9	283.6	174.4
92.9	615.0	20.7	141.0	7.6	47.0	34.5	200.0	
±14.78		±3.98		±1.83				
86.4	666.4	22.4	172.0	7.9	61.2	55.2	225.0	208.1
76.1	556.0	20.8	152.0	8.1	59.0	56.0	200.0	
±25.25		±7.31		±2.69				
86.2	683.8	21.1	165.7	7.8	61.4	45.4	275.0	208.8
80.1	657.0	23.2	182.0	9.4	71.0	44.0	300.0	
±17.11		±6.17		±2.56				
72.9	671.3	17.3	158.8	6.4	58.8	43.2	342.5	200.0
74.7	673.5	16.6	151.5	6.4	58.0	42.0	385.0	
±10.06		±3.63		±1.73				

first year, but most particularly during the first 5 months of life. Many points were found to be outside the 95 per cent confidence intervals, indicating that the mean was easily influenced by single values. The location of averages, however, does serve to project certain trends in point of time.

There was a moderate decrease of blood volume from birth to 6 weeks of age, when the value was 96.9 ml.

TABLE II. PREMATURE BABIES (3 OR MORE TESTS)

SUBJECT	SEX	BIRTH WEIGHT (GM.)	AGE AT TEST	WEIGHT AT TEST (GM.)	HEMOGLOBIN (GM./100 ML.)	HEMATOCRIT (PER CENT)	PLASMA VOLUME (ML./KG.)	BLOOD VOLUME (ML./KG.)	RED BLOOD CELL VOLUME (ML./KG.)	HEMOGLOBIN MASS (GM./KG.)	SERUM IRON (μG %)
1	M	2,010	1.7 wk.	2,012	15.3	46.0	59.3	95.7	36.4	14.6	98
(250 mg. IM iron at 50 wk.)			46.6	9,180	6.7	27.0	49.8	64.2	14.3	4.3	17
			50.6	9,250	5.8	23.0	57.3	70.8	13.4	4.1	17
			52.0	9,300	10.3	32.0	62.2	84.6	22.4	8.7	28
2	M	1,200	15.7 wk.	4,660	9.7	27.0	40.8	52.5	11.7	5.1	61
			28.7	5,360	8.3	27.0	59.7	76.9	17.2	6.4	33
			36.7	6,020	7.2	29.0	77.6	102.1	24.5	7.3	38
3	F	1,850	3.0 hr.	1,850	20.8	65.0	56.5	122.1	65.6	25.4	--
			6.0 da.	1,770	17.0	50.0	66.1	112.7	46.6	19.2	--
			4.0 wk.	2,540	10.5	32.5	72.4	99.1	26.6	10.4	--
8	M	2,120	6.0 da.	2,330	15.8	45.0	54.2	86.2	32.1	13.6	111
			15.4 wk.	5,660	11.9	33.0	65.5	90.1	24.6	10.7	97
			28.4	7,560	11.5	34.0	50.9	70.8	19.9	8.1	83
10	F	1,350	14.1 wk.	4,380	8.5	27.0	63.1	81.3	18.1	6.9	22
			36.1	5,720	9.8	36.0	58.3	82.9	24.7	8.1	36
			44.1	5,840	9.7	33.0	64.8	89.2	24.3	8.6	59
11	F	2,140	1.3 wk.	2,170	14.3	40.0	65.8	98.2	32.5	14.1	53
			13.4	4,820	10.2	29.5	52.6	69.6	17.0	7.1	47
			21.4	5,720	9.0	29.0	65.3	85.8	20.6	7.7	41
			25.4	6,280	8.5	26.0	78.6	100.0	21.5	8.5	42
			38.6	7,060	8.0	28.0	85.8	111.7	25.8	8.9	33
			46.6	7,580	8.1	30.5	87.0	116.3	29.3	9.4	50
14	F	2,350	5.0 da.	2,220	16.6	63.0	48.4	101.0	52.6	16.8	156
			6.9 wk.	3,260	11.3	31.5	68.8	93.1	24.2	10.5	166
			14.9	4,520	10.9	26.0	51.2	65.2	14.0	7.1	58
			22.9	5,750	12.0	36.0	56.3	80.1	23.8	9.6	88
			48.9	7,880	10.6	30.0	55.4	73.6	18.3	7.8	44
16	M	1,920	5.0 da.	1,920	17.2	49.5	67.4	114.2	46.7	19.6	111
			13.6 wk.	4,660	9.3	28.0	67.4	87.7	20.3	8.2	41
			17.6	5,480	10.0	31.0	51.5	69.2	17.7	6.9	28
			22.6	6,350	9.8	32.0	59.9	81.5	21.5	8.0	36
			44.6	9,600	9.4	31.0	51.6	69.4	17.8	6.5	61
18	F	1,980	3.0 da.	1,780	13.2	40.0	83.4	124.6	41.2	16.5	64
			5.4 wk.	2,820	9.4	24.0	81.6	101.8	20.2	9.6	81
			15.4	4,440	9.8	29.5	62.6	82.8	20.2	8.1	74
			26.4	5,460	8.5	28.0	50.7	65.9	15.3	5.6	34
			31.4	4,900	8.4	29.0	75.9	99.9	23.9	8.4	50

			31.4	4,900	8.4	29.0	75.9	99.9	23.9	8.4	50
19	F	1,960	2.0 da.	1,900	17.3	52.0	52.5	92.1	39.6	16.0	103
			5.4 wk.	3,200	8.9	24.0	66.3	82.8	16.4	7.4	64
			11.4	4,560	9.8	29.0	67.9	89.3	21.4	8.8	78
20	F	2,100	4.0 da.	2,120	17.0	51.0	45.8	79.1	33.3	13.4	100
			3.0 wk.	2,670	11.1	35.0	46.5	65.4	18.9	7.3	108
			7.4	3,860	9.6	26.0	66.7	85.0	18.3	8.2	89
			11.7	4,680	11.1	32.0	67.6	91.9	24.3	10.2	53
			17.9	5,820	11.6	34.0	51.3	71.3	20.1	8.3	77
22	F	1,630	2.4 wk.	1,570	14.2	44.0	90.6	142.4	51.8	20.2	131
			10.9	3,490	9.2	28.0	100.5	130.7	30.3	12.0	89
			39.6	7,000	6.3	23.0	82.2	101.5	19.3	6.4	11
23	F	1,500	1.1 wk.	1,420	17.2	56.0	75.4	140.4	65.0	24.2	--
			10.9	3,580	9.7	31.5	75.1	101.6	26.4	10.0	67
			39.6	7,300	6.8	24.0	74.9	93.5	18.5	6.4	23
24	M	1,658	9.4 wk.	4,030	9.0	29.0	56.3	74.1	17.8	6.7	66
(250 mg. IM iron at 36 wk.)			16.4	4,470	10.4	31.0	64.5	86.8	22.2	9.0	36
			20.4	5,540	9.8	32.0	53.5	72.8	19.2	7.1	50
			36.1	7,460	7.3	26.5	44.5	57.0	12.5	4.2	33
			46.3	7,800	9.7	29.0	74.2	97.6	23.4	9.5	14
25	M	2,090	1.0 wk.	2,100	15.6	47.0	66.9	109.5	42.5	17.1	111
(150 mg. IM iron at 48 wk.)			8.1	3,810	10.0	29.0	72.1	94.9	22.7	9.5	78
			32.0	7,600	5.9	27.0	48.1	62.0	13.8	3.7	26
			46.0	8,960	5.0	19.0	61.5	72.9	11.5	3.6	34
			51.1	9,540	8.9	30.0	43.4	57.7	14.3	5.1	72
28	M	1,700	4.4 wk.	2,180	11.2	32.0	74.4	101.1	26.7	11.3	116
			10.3	3,160	9.8	28.0	95.8	124.6	28.8	12.2	64
			18.4	4,600	8.9	28.5	95.3	124.7	29.4	11.1	36
			41.4	8,120	9.2	32.0	98.0	133.2	35.2	12.3	44
			51.3	8,800	9.7	29.0	59.8	78.6	18.9	7.6	56
29	F	1,445	4.4 wk.	2,200	13.6	40.5	65.4	98.2	32.9	13.3	144
			10.3	3,100	9.8	29.0	116.9	153.8	36.9	15.1	111
			19.2	3,960	11.4	37.0	82.5	118.9	36.4	13.6	44
			46.9	6,740	10.6	34.0	71.0	98.7	27.7	10.5	103
30	M	2,240	6.0 da.	2,360	15.6	45.0	37.2	59.2	22.0	9.2	114
			10.7 wk.	4,020	10.6	31.0	55.9	75.2	19.3	8.0	22
			14.7	4,720	10.6	32.0	54.6	74.2	19.6	7.9	42
			34.7	6,960	5.6	22.0	70.9	86.6	15.7	4.9	44
31	M	1,320	2.6 wk.	1,820	13.8	40.0	59.0	88.1	29.1	12.1	139
			11.6	3,700	11.1	30.0	61.7	82.0	20.4	9.1	78
			17.7	4,980	9.7	29.5	52.4	69.2	16.9	6.7	44
			33.6	6,640	11.6	34.0	58.8	81.8	23.0	9.5	33
			42.6	7,300	10.6	33.0	55.4	76.1	20.8	8.1	56

TABLE II (CONT'D)

SUBJECT	SEX	BIRTH WEIGHT (GM.)	AGE AT TEST	WEIGHT AT TEST (GM.)	HEMOGLOBIN (GM./100 ML.)	HEMATOCRIT (PER CENT)	PLASMA VOLUME (ML./KG.)	BLOOD VOLUME (ML./KG.)	RED BLOOD CELL VOLUME (ML./KG.)	HEMOGLOBIN MASS (GM./KG.)	SERUM IRON (μG %)
32	F	1,380	5.4 wk.	2,000	10.8	30.0	84.4	112.3	27.9	12.1	164
			13.3	3,810	8.5	28.5	76.4	100.0	23.5	8.5	67
			16.0	4,140	8.3	24.0	95.4	119.0	23.6	9.9	59
			30.3	7,300	9.7	30.0	69.0	91.8	22.8	8.9	20
34	M	1,300	3.7 wk.	1,700	12.0	38.0	91.1	132.8	41.7	15.9	80
			17.1	4,480	6.8	20.0	69.7	83.5	13.8	5.7	36
			37.9	6,400	8.5	25.0	70.5	88.8	18.3	7.6	38
37	M	1,390	6.1 wk.	1,810	8.8	24.0	74.9	93.4	18.5	8.2	122
(12 mg. Fe P.O. per day at 30 wk.)			20.3	4,320	7.7	28.0	44.6	58.1	13.4	4.5	29
			36.3	7,000	11.8	27.0	72.1	92.9	20.7	11.0	75
39	F	2,100	1.7 wk.	2,000	17.2	50.0	71.9	122.6	50.7	21.3	175
			16.6	5,020	11.6	33.0	55.1	75.8	20.7	8.8	42
			28.9	7,900	10.7	30.5	51.7	69.1	17.4	7.4	41
40	M	1,700	3.1 wk.	2,300	12.7	39.0	55.8	82.4	26.6	10.5	115
(200 mg. IM iron at 30 wk.)			30.0	5,410	7.6	27.0	48.9	62.9	14.0	4.8	33
			35.4	6,680	11.0	34.0	59.3	82.5	23.2	9.1	--
			47.4	8,200	12.0	35.0	56.9	80.1	23.2	9.6	56
45	M	1,920	1.1 wk.	1,760	17.0	48.0	48.1	79.7	31.6	13.5	--
			10.1	4,100	8.7	24.0	60.6	75.6	15.0	6.6	64
			15.7	5,490	9.8	28.0	78.0	101.5	23.5	9.9	67
			30.3	7,460	10.0	32.0	52.7	71.7	19.0	7.2	90
46	M	1,820	1.3 wk.	1,870	18.6	54.0	48.1	86.8	38.8	16.1	--
			10.1	4,440	9.4	24.5	62.9	78.8	16.0	7.4	72
			15.7	5,710	10.0	30.0	63.6	84.6	21.0	8.5	44
			30.3	7,420	10.2	32.0	41.5	56.4	14.9	5.8	63
50	M	1,900	1.3 wk.	1,980	14.2	47.0	60.6	99.1	38.5	14.1	61
			3.1	2,310	10.6	33.0	73.4	100.9	27.5	10.7	90
			7.6	2,900	9.6	28.0	81.4	105.9	24.5	10.2	66
			13.3	3,680	9.3	27.0	76.1	97.9	21.9	9.1	42
51	F	1,725	1.3 wk.	1,660	14.5	44.0	91.9	144.4	52.5	20.9	86
			3.1	2,020	9.7	28.5	80.0	104.7	24.7	10.1	87
			7.6	2,940	8.8	24.5	51.3	64.3	13.0	5.6	60
			13.3	4 215	9.8	28.0	57.2	74.4	17.2	7.3	55

per kilogram. Between 6 and 10 weeks of age there was no significant change, but this was followed by an abrupt decline to 80.1 ml. per kilogram by 15 weeks of age. By 19 weeks, an increase to 85.5 ml. occurred, accentuated by the high values encountered in Subjects 28, 29, and 32. By 27 weeks, the blood volume had dropped to an average of 76.5 ml. per kilogram, and this value was maintained until 32 weeks. An increase to 90.3 ml. was observed by 38 weeks. The volume remained at a level of about 86 ml. per kilogram between 40 and 47 weeks, but this was reduced to 73 ml. at 52 weeks of age.

It was interesting to note that some of the infants (3, 10, 11, 19, 34, and 50) had relatively stable blood volumes as they aged, whereas others (1, 2, 8, 14, 16, 20, 24, 25, 29, 37, 39, and 46) had fluctuating blood volumes. Samples of blood for volume measurements were drawn in the morning so that these variations were not diurnal, nor did change in season appear to have an influence.

It was apparent that at least after 20 weeks of age the range of values in these premature infants was smaller than in full-term infants.[1] Also, a greater uniformity of blood volume from one observation to another was noted.

The total blood volume increased, roughly, in relation to weight, and of weight to age.

Fig. 2 illustrates the poor relationship between the blood volume and the venous hematocrit. The correlation coefficient was 0.24, indicating that the blood volume is independent of the hematocrit from birth through the first year of life. Fig. 3 demonstrates the rather unusual change of relationship between the total blood volume expressed in milliliters and the venous hematocrit in the neonatal period and after. When the blood volume ranged between 140 and 260 ml., the hematocrit ranged from 23 to 65 per cent. On the other hand, when the infants were no longer neonates and the total blood volumes ranged from 270 to 1,080 ml., the hematocrit values were in a more narrow range (19 to 37 per cent).

The observations in Subjects 3, 22, 23, 28, 29, and 32 are examples of expanded blood volume, and those in Subjects 1, 14, 24, 37, 46, and 51 are examples of contracted volume at some time during the first year of life (see Table II). When such states of hypo- or hypervolemia occur, paradoxical values of hemoglobin concentration and hematocrit are encountered. This is illustrated by the data from Subject 2. In this infant, between 15 and 36 weeks of age, the total blood and erythrocyte volumes had doubled and the circulating hemoglobin mass increased by 43 per cent. Despite this, the hemoglobin concentration decreased 26 per cent and the hematocrit remained virtually unchanged.

Plasma Volume.—In the first 2½ months there was a tendency for the plasma volume to increase as the erythrocyte volume decreased. The total blood volume, although declining in this period, was thus maintained at a fairly high level due to the expansion of the plasma compartment. After 10 weeks of age, the mean plasma and total blood volumes were parallel.

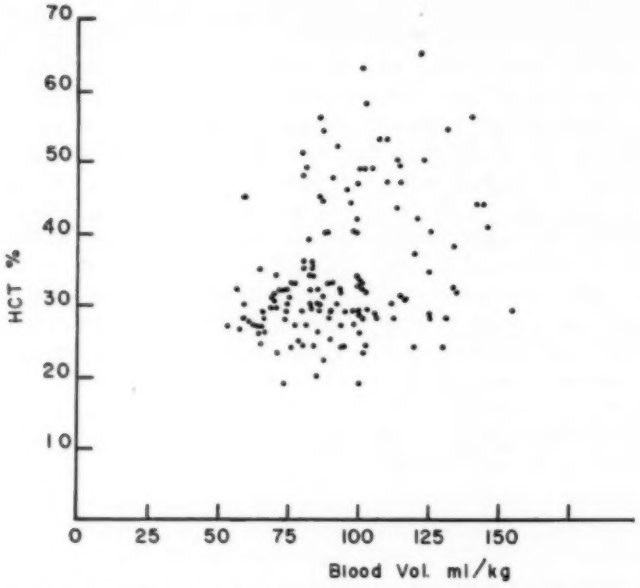

Fig. 2.—The relationship of blood volume based on body weight and venous hematocrit is demonstrated. Individual points above 40 per cent hematocrit were observed in the neonatal period. Then as later there was poor correlation of the values. The coefficient of correlation was 0.24.

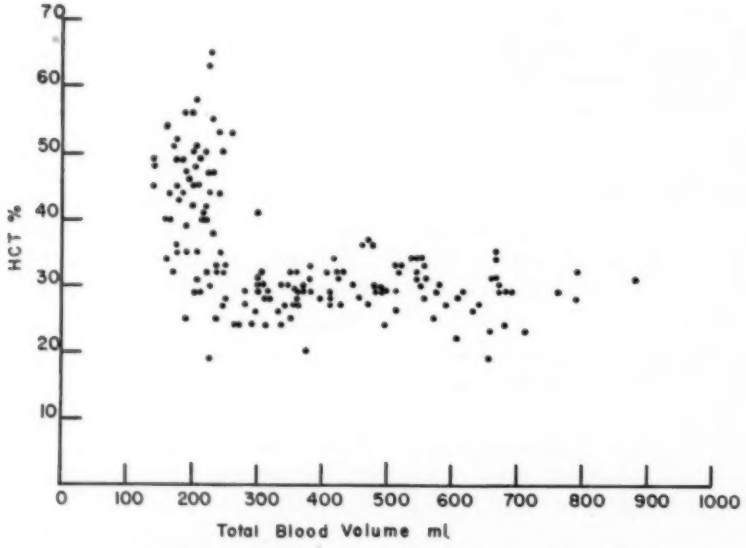

Fig. 3.—The relationship of total blood volume and venous hematocrit was unusual. Blood volumes in a range between 150 and 250 ml. (neonatal period) were observed with hematocrit values of very widespread range, approximately 23 to 65 per cent. Relatively narrow range of venous hematocrit (20 to 35 per cent) was observed with blood volumes between 250 and 900 ml. when the infants were beyond the neonatal period.

An average plasma volume of nearly 60 ml. per kilogram was observed in the first week, increasing to 73 ml. by the eleventh week. Between 14 and 32 weeks of age, the average volume was close to 60 ml. per kilogram. A moderate increase to nearly 70 ml. occurred by the thirty-eighth week, followed by a decline to 65 ml. at 46 weeks. A further and more abrupt decrease to 55 ml. per kilogram occurred between 46 and 52 weeks.

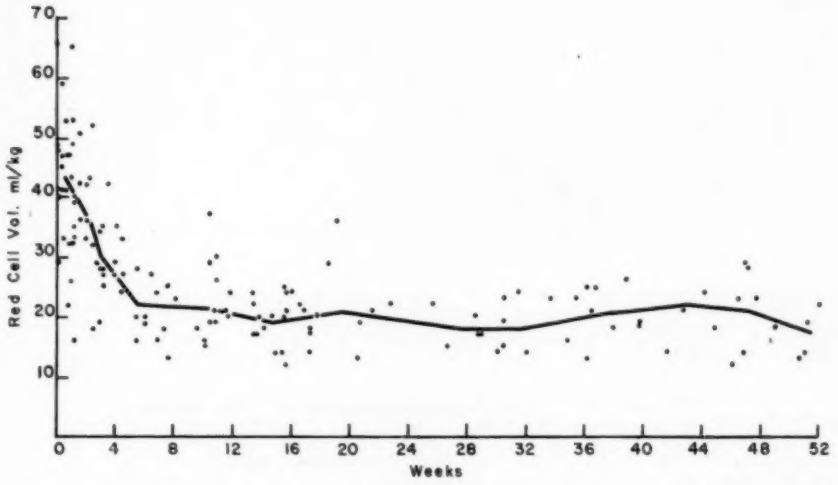

Fig. 4.—Individual values for erythrocyte volume are plotted against age in weeks in this figure. The heavy line denotes the means from birth to 52 weeks of age. The average volume from 12 to 52 weeks was near the level of 20 ml. per kilogram, but fairly wide deviations were recorded.

An interesting observation was made that there was an increase in plasma and erythrocyte volumes in 4 infants treated with medicinal iron. Further studies are needed to demonstrate the possible significance of this finding.

Erythrocyte Volume.—Fig. 4 illustrates the individual and average erythrocyte volumes of the subjects plotted against the age in weeks.

The mean volume in the first 2 days of life of 6 infants was 45.5 ml. per kilogram, a value 5 ml. higher than reported in full-term infants.[1] The average volume was reduced by half at 6 weeks of age, to a value of 23.5 ml. per kilogram. A more modest decline to 18 ml. per kilogram was observed by 14 weeks, followed by an increase to 21 ml. at 19 weeks. This rise in the mean value was influenced by the very high erythrocyte volumes of Subjects 28 and 29 at 18 to 19 weeks of age.

The average erythrocyte volume was 16 ml. per kilogram at 27 weeks of age, remained at that level until 31 weeks, and then increased to slightly over 20 ml. at 48 weeks. A subsequent decrease to 17 ml. by the fifty-second week was noted.

It may be stated that, in general, the average erythrocyte volume of the premature infants in this study deviated

very little from a level of 20 ml. per kilogram between 12 and 52 weeks of age. This stability is more apparent than real since variations about the means were rather wide.

original mean of 20.5 Gm. per kilogram on the first day of life, the hemoglobin mass decreased to a value of 10 Gm. per kilogram at 6 weeks of age. A more gradual decline to 7.9 Gm. at 15

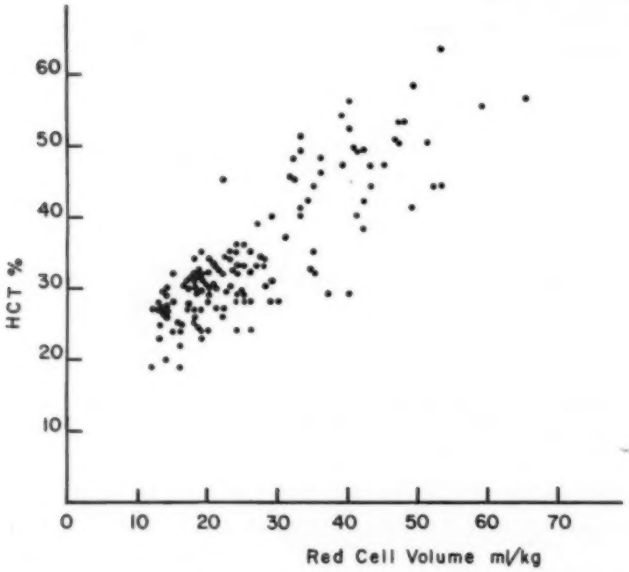

Fig. 5.—The erythrocyte volume in millimeters per kilogram of body weight is plotted against the venous hematocrit in this figure. The relationship of these values was poor except in a very narrow range in both the neonatal period and in succeeding weeks. The coefficient of correlation was 0.54.

Fig. 5 illustrates the poor relationship of venous hematocrit to erythrocyte volume. Significant correlations were not found in the neonatal period nor in the later months of life. The relationship was seen to be closer in these premature infants, however, than in full-term infants.[1] The coefficient of correlation of these values was 0.54.

Circulating Hemoglobin Mass.—Fig. 6 illustrates the individual and average hemoglobin mass values expressed in grams per kilogram of body weight, plotted against age in weeks. From an

weeks was observed. An insignificant rise to 8.4 Gm. at 19 weeks was followed by a further decline to 6.7 Gm. by 32 weeks of age. The average mass rose to 7.7 Gm. per kilogram at 37 weeks, and this value was closely maintained for the next 10 weeks. Between 48 and 52 weeks, the average value decreased to 6.4 Gm. per kilogram.

Fig. 7 demonstrates the relatively poor correlation between the hemoglobin concentration and the circulating hemoglobin mass. In the neonatal period, as later, considerable scatter was noted. The extremes of either value

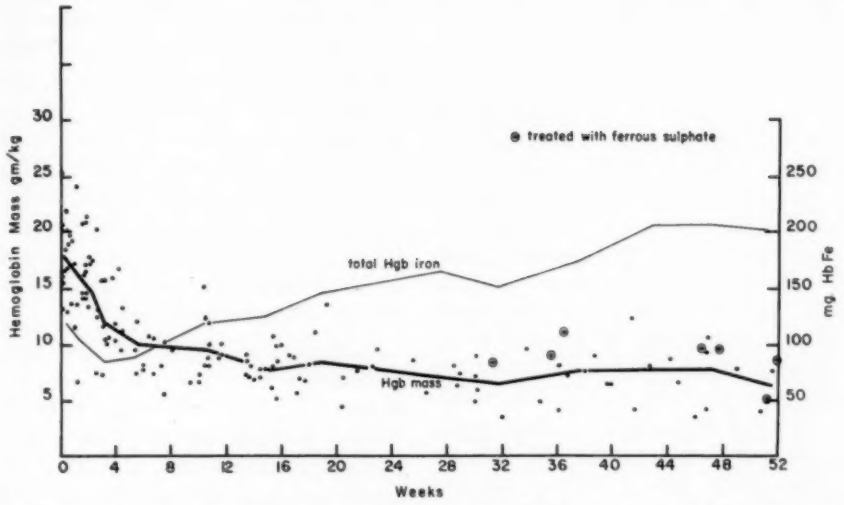

Fig. 6.—Individual values of hemoglobin mass based on body weight are plotted against age in weeks in this figure. The heavy line denotes the mean circulating mass. Circled points indicate the position of hemoglobin mass in infants treated with medicinal iron (see Table II). The thin line represents average values of total hemoglobin iron, calculated from the circulating hemoglobin mass. The lowest value was recorded in the third week. The neonatal level was regained by 10 weeks of age.

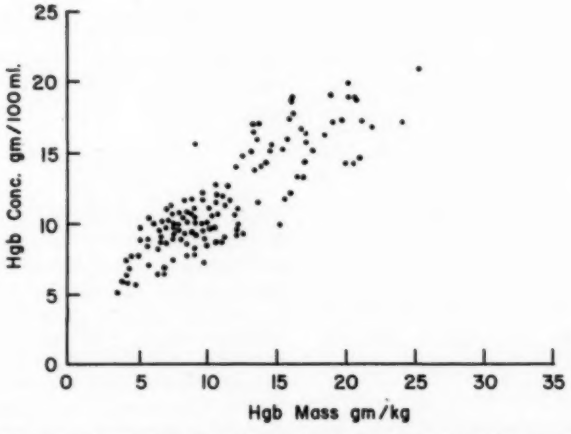

Fig. 7.—This figure illustrates the relationship between hemoglobin concentration and circulating hemoglobin mass (based on body weight). The coefficient of correlation was 0.60, indicating only a narrow relationship.

were most closely related one to the other. The coefficient of correlation of these values was 0.60.

Total Hemoglobin Iron.—The average values of total hemoglobin iron are illustrated in Fig. 6. The original mean of the first week after birth was 119 mg. A value of 85 mg. was observed in the third week, and at the sixth week this had not changed to a significant degree. By the tenth week, the hemoglobin iron had increased to 119 mg. the value of the first week. Similar resumption of neonatal levels was not seen in full-term infants until the sixteenth week of life.

Gradual increments of total hemoglobin iron were recorded until 28 weeks of age when a level of 164 mg. was reached. A decrease to 150 mg. was found at 32 weeks, followed by a more rapid increase to 173 mg. by 37 weeks of age. This last increment was greater than those preceding because medicinal iron given to a few infants boosted their individual hemoglobin content. At 43 weeks of age, the hemoglobin iron was 207 mg. This value was sustained until 47 weeks. The level of 201 mg. recorded in the fifty-second week is not a significant decrease.

Serum Iron and Iron-Binding Capacity of the Serum.—The average concentration of iron in the serum at birth was high and remained so during the first 8 weeks. Thereafter, the concentration fell to its lowest level between 35 and 40 weeks of age. Moderate increments thereafter were influenced by the administration of iron to a few of the infants.

The mean iron-binding capacity of the serum was zero, or nearly so, in the first week of life. Zero capacities were encountered sporadically through the first 4 weeks. Average values increased on the whole through the year. The iron saturation of the serum was thus found to decrease from 87 per cent in the first week after birth to 11 to 14 per cent in the twelfth month. This was believed to indicate a general depletion of iron stores but not iron-deficiency anemia, since this condition could be diagnosed in only 2 of the 11 infants studied at that age.

It was interesting to note that total hemoglobin iron remained almost stationary in some infants for many weeks. The administration of medicinal iron then resulted in marked increases of total hemoglobin iron but not, in each case, of the serum iron concentration. This was believed to indicate that the value of serum iron was more a token of the replenishment of tissue iron stores than of the assessment of anemia.

The development of iron depletion and anemia and the response to treatment is illustrated in the following cases.

CASE REPORTS

Case 1 was anemic by 46 weeks of age. At 50 weeks he was given 250 mg. of iron-dextran,* intramuscularly. A marked increase of blood elements was observed by 52 weeks of age. This healthy infant had grown rapidly and, although on an adequate diet, had apparently been unable to assimilate enough iron to maintain optimal hemoglobin formation. In time he had developed a microcytic hypochromic anemia. Once iron was made freely available through parenteral administration it was rapidly utilized.

*Imferon, Lakeside Laboratories, Milwaukee, Wis.

Case 18 developed a mild iron-deficiency anemia by 26 weeks of age. This spontaneously improved by 31 weeks. It was assumed that absorption of iron from the diet increased when tissue demands became marked, and that this resulted in an increased utilization and consequent reversal of the process of iron depletion. No medicinal therapy was given to this infant.

Case 25 demonstrated another instance of the development of iron deficiency in a rapidly growing infant. At 32 weeks of age, anemia was already well advanced. At 48 weeks, 150 mg. of iron* was given (intramuscularly). Again, a prompt response to treatment was observed.

Case 37 had a low birth weight of 1,390 grams. It was expected that this infant might develop a frank anemia early in life. By 20 weeks of age, a profound reduction of hemoglobin mass was recorded. An iron preparation was given orally at 30 weeks of age in a dose equivalent to 12 mg. of elemental iron per day. This was continued until 36 weeks when an excellent response was observed. There was no indication of an impairment of intestinal absorption of iron. Rapid growth of this infant and minimal reserves of iron had combined to produce an early depletion of iron and consequent anemia.

COMMENT

The blood volume of the premature infants studied at or near birth was slightly greater than that recorded by us in full-term infants.[1] Through the first year of life the values were comparable in both premature and full-term infants, with similar deviations about the means.

The reduction of erythrocyte volume in early weeks in the premature infants did not result in a proportionate contraction of the total blood volume. This was due to the increase in plasma. The blood volume, in effect, was maintained at a relatively high level despite the rapid constriction of the volume of circulating erythrocytes.

The total red cell volume usually reached its lowest levels between 3 and 7 weeks of age. By 10 weeks, the total volume equaled that at birth. As expected, the total circulating hemoglobin mass was also at its lowest levels between 3 and 7 weeks. The total hemoglobin iron was observed to be at a minimum between 3 and 4 weeks and to have increased slightly by 6 weeks of age. At 10½ weeks, neonatal values were regained. These results suggest that erythropoiesis became active between 3 and 7 weeks after birth.

In the first month of life the hemoglobin iron of the infants was reduced 35 mg. on the average, or 29 per cent. This amount was re-embodied in the erythrocytes by 10 weeks of age. Until the tenth week, the cells contained an amount of iron exactly proportionate to that of the cells at birth. Following the tenth week, the content of hemoglobin iron in the erythrocytes was gradually reduced. These results indicate that the iron stores at birth were adequate for hemoglobin synthesis until only about 10 weeks of age.

Demands for iron from the rapid growth, so characteristic of the premature infant, are seldom met by diet alone in the first months of life. It is hardly remarkable, then, that evidence of iron depletion should appear in these early months.

Woodruff[10] has demonstrated that low birth weight will often lead to the development of iron-deficiency anemia. Examples may be found in this study where low birth weight in itself did not

predispose to such a condition. Subjects 10, 29, 31, and 32, who weighed between 1,320 and 1,500 grams at birth, were without evidence of anemia for as long as they were followed. Subjects 29 and 32 were of high birth order, and 29 a twin. On the other hand, Subjects 1, 25, and 30 (birth weights 2,010, 2,090, and 2,240 grams, respectively) did develop anemia at some point during the investigation. It may be supposed that some infants, regardless of birth weight, have a superior ability to absorb and utilize dietary iron, and that birth weight more closely approaching full-term values does not assure a greater freedom from the development of anemia. The demands for iron are quite as insistent whether the initial weight at birth is low or high in the premature range.

It is evident from this study that an exogenous source of iron may be required by the premature infant earlier than 3 months of age, as is currently believed. In the first year of life one cannot predict the intrusion of episodes of severe infection or periods of dietary inadequacy which may lead to more pronounced iron deficiency. Even without these and other influences, iron depletion, if not frank anemia, is common. On the basis of information from this and other studies,[12, 13] we suggest the routine prophylactic oral administration of iron to premature infants, starting between 4 and 6 weeks of age. At this institution, a dose of 7 mg. daily of elemental iron is prescribed. The indiscriminate use of parenteral iron preparations is inadvisable. Instances do occur, however, when the ingestion of oral iron is difficult owing to gastric intolerance, lack of follow-up medical care, or lack of patient reliability. Parenteral administration is then preferred.

It was concluded from the results of a study of dietary iron in premature infants[11] that if iron is supplied in the first weeks of life it will be utilized before the third month. Recent studies by Hammond[12] have demonstrated this to be true when the iron source is parenteral and administered in the first week after delivery.

The blood volume of some infants (1, 24, 37, and 40) was contracted at the time iron deficiency was diagnosed. The institution of iron therapy was accompanied by an expansion of the plasma and total blood volumes as well as the erythrocyte volumes. This situation did not obtain in Case 25 whose erythrocyte volume increased but whose plasma and blood volumes were reduced. It has been observed in full-term infants[1] that expansion of both plasma and erythrocyte compartments of the total blood volume may take place with recovery from iron deficiency. The possible significance of this finding is obscure.

Considerable variations about the mean blood, plasma, and erythrocyte volumes were observed from birth to the end of the first year of life. It is obvious that average values are not completely dependable in this period of infancy. These deviations were recorded whether determinations were made singly or serially. Therefore, we wish to point out that, in trying to establish values of this nature for premature infants, derived figures are not securely founded and that limitations of the method of determining blood volume from plasma volume should not be ignored. We consider that caution

must be exercised in interpreting estimated values, although it is quite proper to project trends and developments, particularly as they may apply to iron metabolism.

SUMMARY

One hundred and forty-five plasma volume determinations were performed on 51 healthy premature infants between birth and 1 year of age. Two or more serial observations were made on 38 of the infants. Plasma volumes were measured with the use of T-1824. Serum iron and iron-binding capacity determinations were also made.

The average blood volume at birth was found to be 109 ml. per kilogram, a value slightly higher than in full-term infants. In the first 2½ months of life there was a tendency for the plasma volume to increase as the erythrocyte volume decreased. This had the effect of maintaining the total blood volume at a relatively high level.

The erythrocyte volume at birth was 45.5 ml. per kilogram (about 5 ml. higher than in full-term infants) and was close to 20 ml. per kilogram between 12 and 52 weeks of age. There was no significant correlation between erythrocyte volume and growth gain, nor between erythrocyte volume and venous hematocrit. Normal growth increments far outdistanced the expansion of erythrocyte volume.

The circulating hemoglobin mass was 36.5 Gm. in the first 2 days of life; it declined 33 per cent by 4 weeks of age. At 12 weeks it was again at the value recorded in the first 2 days. Further increments were more gradual. On the basis of body weight, an abrupt fall from 20.5 Gm. per kilogram at birth to 10 Gm. at 6 weeks occurred. The average value remained between 6.4 and 8.0 Gm. per kilogram for the rest of the year. There was poor correlation between the values for hemoglobin concentration and circulating hemoglobin mass in both the neonatal period and later. The total hemoglobin iron reached its lowest level between 3 and 6 weeks of life. By the tenth week, values recorded in the first week were regained. It was concluded that erythropoiesis became active between 3 and 7 weeks after birth and that the original iron stores were adequate for hemoglobin synthesis until only about 10 weeks after birth. This explains in part the development of iron depletion and iron deficiency at an earlier age in the premature infant than in the full-term one.

The results of this investigation indicate the average values of total blood, plasma, and erythrocyte volumes and of circulating hemoglobin mass of premature infants from birth through 1 year of age. It was concluded that within the limitations of the techniques used, these values are representative of an urban clinic group.

It was observed that considerable variation about the mean values was present throughout the year. The average values, therefore, indicate changes that may be expected in the first year of life but should be considered specific in only a restricted sense.

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". . . Mark my words: if no governmental inspection is ever instituted, the time will come in many rural districts when vaccination will degenerate into desuetude. It is not worth the parish surgeon's while to ride—

'O'er hill and dale, o'er moss and moor,'

to have a two-handed clack with some ignorant woman, and endeavor to talk down all her anti-vaccination nonsense. . . ."

Signed,

"A Public Vaccinator With His Hands Tied."
Letter to the Editor. British Medical Journal, June 25, 1859.

CONGENITAL NEUROCUTANEOUS SYNDROMES IN CHILDHOOD

II. Tuberous Sclerosis

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TUBEROUS selerosis is a congenital disorder in which tumorlike masses are found in many organs of the body. The lesions are not confined to tissues of a single germinal layer. Those of the brain and skin are ectodermal, while those of other organs, such as the kidneys, heart, and lungs, are mesodermal in origin. The disease occurs in all races and affects both sexes. The cerebral lesions are responsible for the neurologic symptoms. There are several types of cutaneous manifestations, but the characteristic facial lesion, adenoma sebaceum, is pathognomonic. The internal organ visceral involvement is usually asymptomatic.

The etiological diagnosis is often overlooked in the early stage of this disease when seizures are the only symptoms. The mental status is difficult to appraise in early infancy and minor changes in the skin are often considered insignificant.

At The Blue Bird Clinic, 8 cases of tuberous sclerosis have been seen since 1951. All of these patients were brought to the clinic with the chief complaint of seizures. The diagnosis of tuberous sclerosis was readily made in 2 patients in whom the classical clinical picture was present. In the other 6 children the etiological diagnosis was not made until they developed adenoma sebaceum during observation. In retrospect, however, a variety of other cutaneous manifestations such as depigmented areas, café au lait spots, plaques, etc., had been noted before the appearance of the characteristic facial lesions. These earlier skin changes should therefore arouse suspicion of such a diagnosis.

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HISTORICAL

In 1880,[2] a French neurologist, Bourneville, reported the case of a 14-month-old infant who had had focal seizures since birth. Skin lesions were observed on the face, but their significance was not appreciated. In a series of publications between 1880 and 1900,[2] he described 10 cases of mental deficiency associated with the presence of "potatolike" nodules in the brain. This condition he called "tuberous sclerosis."

Balzer and Menetrier,[4] in 1885, described a symmetric condition of the face consisting of flesh-colored, discrete papules which they called "adenoma sebaceum."

Five years later, in 1890, Pringle,[5] an English dermatologist, reported

patients with facial lesions of firm, whitish- or sago-grain-colored solid plaques and nodules in typical butterfly distribution over the nose and nasolabial fold. These lesions were identical to the "adenoma sebaceum" described by Balzer and Menetrier.

The relation between the skin lesions and cerebral tuberous sclerosis was clearly recognized by Vogt,[6] who, in 1908, introduced the triad of epilepsy, mental deficiency, and adenoma sebaceum as a clinical entity. The term "epiloia" applied by Sherlock in 1911[7] should not be used as it was merely an artificial compounding of the words epilepsy and aloia (mindlessness in Greek).

The heredofamilial aspect of this disorder was first recognized in 1913 by Berg,[8] who reported 3 cases in 3 successive generations in one family.

Van der Hoeve[9] was the first to define the true nature of retinal lesions in this disease. He described them as tumors originating in the nerve fiber layer, not as sequelae of an inflammatory process as had been previously thought. He called them "phakomata" (Greek "phakos" meaning the mother spot) as they are closely related to congenital moles.

ETIOLOGY

Tuberous sclerosis is a developmental anomaly. The occurrence of the disease in families has been reviewed by Dickerson,[10] Jordan,[11] Shelmire,[12] and others. Fabing[13] reported the occurrence of tuberous sclerosis in identical twins. In the same family some individuals may exhibit the typical clinical picture, while others have rudimentary or incomplete manifestations, e.g., epilepsy, adenoma sebaceum, retinal tumors, and renal tumors, alone or in various combinations. The manner in which tuberous sclerosis is inherited is not certain although it is thought to be by irregular dominance.[14]

PATHOLOGY

Tissues of ectodermal origin, particularly the brain, skin, and retina, as well as tissues of mesodermal origin, are involved in the defective development with overgrowth of fibrous and vascular elements resulting in tumefaction and fibrosis.[15] The anatomic changes begin early in embryonic life but do not terminate at birth.[16] Though it does not seem likely that new foci of disease develop after birth, preformed foci are capable of further growth and may not become manifest for some time after birth, at puberty or even later.

The Brain.—In the brain the lesions of tuberous sclerosis are smooth, hard, white nodules. They vary in size, shape, number, and distribution.[17] They are most commonly found in the cerebral cortex and the ependymal linings of the ventricles. They may also be found in the subcortex, cerebellum, thalamus, basal ganglia, and brain stem.

Microscopically, there are abnormalities of both the ganglion cells and the glial elements. The nerve cells may be decreased in number, disintegrated, and atrophied. Giant cells are found in and about the tumors. The nerve fibers are irregular and reduced in number.[18] The nodules may undergo cystic degeneration and calcification. Malignant growths may arise in such lesions.[19, 20]

In the nerve fiber layer[21] of the retina there may be solitary or multiple tumor masses composed of glial cells, nerve cells, and blood vessels.

The Skin.—Pringle[5] stated that the skin lesions were primarily neoplasms of the sebaceous glands with an increase in the number and complexity of the glandular structures. However, Jadassohn[21] showed that it was neither an adenomatous nor a hyperplastic condition of the sebaceous glands. Rather, the lesions are nevoid in character and consist mainly of hyperplastic connective and vascular tissue (fibroangiomatous nevi).

SYMPTOMATOLOGY

Typically, a triad of symptoms consisting of epilepsy, mental deficiency, and adenoma sebaceum is seen in fully developed cases of tuberous sclerosis. Any phase of the triad may be manifest alone or any two may occur in the absence of the third.

Seizures.—Seizures generally appear within the first 2 years of life,[25] but they may occur at birth.[26] The onset of seizures in our patients ranged from 1 week to 3½ years of age (Table I). In 5 of our 8 patients seizures appeared within the first year of life. The type of seizure pat-

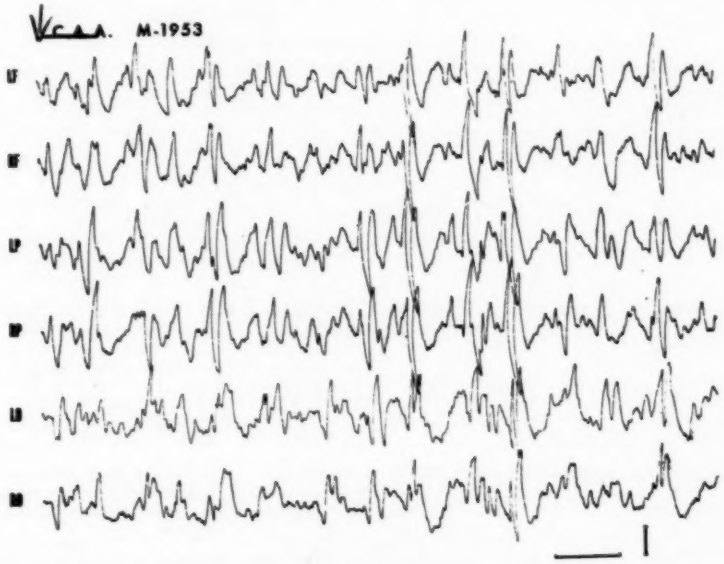

Fig. 1.—Case 2. Electroencephalogram of patient at 2 years of age which shows bursts of generalized spike-wave activity.

Other Organs.—Visceral abnormalities which may coexist are fibroadenoma of the kidney,[22] rhabdomyoma of the heart, and cystic defects of the lungs[23] and of the skeletal system.[24]

tern in these patients is quite variable. In our series massive spasms[27] myoclonic and akinetic attacks were the most common initial seizure types. These patterns are interesting in that

they suggest a subcortical origin of the seizures which is in keeping with the pathologic finding that the lesions most commonly involve the paraventricular and basal ganglion regions. The characteristic electroencephalographic changes of bursts of generalized spike-wave activity are illustrated in Fig. 1. Of interest in this regard is the case reported by Baird, Wycis, and Spiegel[28] in which electrolytic coagulation of the basal ganglia region (where calcification had been demonstrated in roentgenograms of the skull) resulted in the arrest of protracted akinetic seizures.

TABLE I. GENERAL DATA

CASE	PATIENT	SEX/ RACE	AGE AT ONSET OF SEIZURES	AGE FIRST SEEN	AGE AT PRESENT (YEARS)	PRESENTING SYMPTOMS
1	K. K.	M/W	3½ yr.	4 yr.	6 4/12	Akinetic seizures
2	C. A.	F/W	3 mo.	22 mo.	10 8/12	Massive spasms
3	H. F.	M/W	6 mo.	15 mo.	5 10/12	Akinetic seizures
4	M. F.	F/W	6 mo.	7 yr.	9	Massive spasms
5	J. P.	M/W	1½ yr.	5 yr.	8	Absence and myoclonic seizures
6	J. N.	M/C	2 mo.	2½ yr.	3 10/12	Massive spasms
7	W. W.	F/W	2 yr.	15 4/12 yr.	20	Status epilepticus
8	G. B.	M/W	1 wk.	3 mo.	5	Focal motor seizures

TABLE II. CHANGE IN SEIZURES AND ELECTROENCEPHALOGRAM

CASE	AGE AT ONSET	SEIZURES	ELECTROENCEPHALOGRAM	
1	3½ yr.	a. Akinetic; b. massive spasm; c. limpness and pallor	4 yr.:	Continuous slow spike-wave activity
			5 yr.:	Same
2	3 mo.	a. Massive spasm; b. generalized clonic; c. right-sided motor; d. status epilepticus	2 yr.:	Continuous slow spike-wave activity
			3 yr.:	Same
			10 yr.:	Poor organization, poor regulation, paroxysmal slow
3	6 mo.	a. Akinetic; b. akinetic with grin and right-sided jerking	15 mo.:	Paroxysmal multiple spike and sharp wave; multifocal slow wave activity
			2 yr.:	Slow spike focus, left parietal
			4 yr.:	Same
4	6 mo.	a. Massive spasm; b. right-sided focal	7½ yr.:	Paroxysmal slow and 3/second slow bursts, left occipital
5	1½ yr.	a. Myoclonic; b. absence; c. akinetic	5 yr.:	Generalized slow spike wave and independent focus, left occipital
			6½ yr.:	Same, plus bursts of multiple spikes
6	2 mo.	a. Generalized tonic; b. myoclonic; c. massive spasm	2½ yr.:	Modified hypsarhythmia
7	2 yr.	a. Absence; b. generalized clonic, right-sided motor; c. status epilepticus	15 4/12 yr.:	Continuous slow, high-voltage left leads
8	1 wk.	a. Left-sided motor; b. generalized clonic; c. massive spasm; d. akinetic	3 mo.:	Depressed activity right superior central region with focal spike- and sharp-wave activity
			14 mo.:	Hypsarhythmia
			3½ yr.:	Modified hypsarhythmia

The type of seizures described above in the very young child gradually give way to focal cortical seizures or to generalized ones or to convulsive equivalent attacks. The initial seizure pattern and the change in pattern with time are shown in Table II.

Generally, the seizures are difficult to control with medication. Occasionally, long periods of remission may occur spontaneously.

TABLE III. FUNCTIONAL STATUS OF PATIENTS

CASE	PRESENT AGE IN YEARS	MENTALITY	SPEECH	BEHAVIOR	ABNORMAL NEUROLOGIC SIGNS
1	6½	Unaware of environment	Few words	Bangs head, bites hands	Strabismus, hyperreflexia
2	10½	Unaware of environment	None	Wild roaming, wild screaming, bites hands	Hyperreflexia
3	6	Retardation	Understandable	Stubborn	Mild weakness of right hand
4	9	Retardation	Normal	Distractability	
5	8	Deficiency	Nearly normal	Constant hyperactivity	Alternating internal strabismus
6	3 9/12	Unaware of environment	None	Looks at hands, clicks tongue, laughs to self	Left facial weakness
7	20	Unaware of environment	None	Silly giggles	Right hemiparesis, athetoid movements
8	4 8/12	Unaware of environment	None	Hyperactivity	Right hemiparesis and hemiatrophy

TABLE IV. CUTANEOUS MANIFESTATIONS

CASE	ADENOMA SEBACEUM		OTHER SKIN LESIONS		SCALP CHANGES
	TYPE	AGE APPEARED (YEARS)	TYPE	AGE APPEARED	
1	Red, seedlike	5	Café au lait, vitiligo Shagreen plaques	Birth Unknown	Hairless spot, 4 by 5 cm., in left temporal region
2	Red, seedlike, pale nodular type	6 to 7	Hemangioma: right calf, "treated" and right side of face Vitiligo	Birth Unknown	
3	Red, seedlike	2½	Café au lait, vitiligo, shagreen plaques Lymphangioma, left thumb	Unknown Birth	Hairless spot, 3 by 4 cm., in left temporal region
4	Pale nodular	2	Shagreen plaques, vitiligo	Birth	
5	Red, seedlike	5	Café au lait, vitiligo Red plaque	Unknown 4 years	
6	Few red, seedlike	3	Small, brown nodules, 1 to 3 mm., on face and trunk	Unknown	
7	Atypical; skin around nose bumpy	Unknown	Subungual fibroma Shagreen plaque	Unknown Unknown	
8	Mostly pale nodular	5	Vitiligo Café au lait	Birth Unknown	

Mental Deficiency.—Usually the first abnormality to be noted is developmental delay. The degree of mental retardation or deficiency varies greatly. Table III summarizes the mental status of our patients. One patient with an I.Q. of 70 is able to compete in a special class in public school; the remainder of our patients, however, are too defective to be in such classes. The usual course is for the mental defect to increase with age.

Speech.—Speech development may be considerably retarded (Table III). Among our patients, 1 has normal speech, 3 have fragmentary speech, and 4 have never talked.

Cutaneous Manifestations.—

Adenoma sebaceum: This characteristic skin lesion has been reported to be present at birth[29] and in other instances at 6 months of age,[30] but the lesions may appear later. In our patients (Table IV) the skin lesions became evident from 2 to 6 years of age. As mentioned earlier, before the development of these characteristic facial lesions, the patient may exhibit other types of cutaneous changes (vide infra) in early life or at birth. These, however, may be overlooked, or their possible significance may not be appreciated.

The dermatologist recognizes several varieties of adenoma sebaceum. Two types are commonly seen in tuberous sclerosis: the red, seedlike spots (Fig. 2) and the nodular form with the color of normal skin (Fig. 3). Microscopically, the former show an abundance of vascular and telangiectatic elements, and the latter excessive fibrosis.[31] The lesions vary in diameter from 1 to 7 mm. They are usually discrete and symmetrically distributed, chiefly on the cheeks and in the furrows alongside the nose.

In our series only one case (Case 4) presented with typical sebaceous adenoma lesions. Six patients developed the facial lesions subsequent to the initial visit. Five of the 6 patients developed the red, seedlike type of adenoma sebaceum initially.

Case 2 was first seen at 3 months of age. Because of severe mental deficiency and poor control of seizures, she was placed in an institution at 6 years of age, at which time she had only a small red plaque on the right cheek. This was thought to be insignificant. A similar lesion was removed from the right calf at 3 months of age. The case was diagnosed as brain damage of unknown cause. When the patient returned to the clinic in 1958, at 10½ years of age, she had many red, seedlike facial lesions with the typical butterfly distribution and a few pale nodules typical of adenoma sebaceum in the nasolabial folds. The red plaque on the cheek had increased in size. The possibility of tuberous sclerosis had not been thought of before this time.

The parents of our patients have not spontaneously commented on the facial or other cutaneous lesions. When questioned, they usually attribute them to drug rash, heat rash, or insect bites. Our observations indicate that the red type of adenoma sebaceum predominates in the young age.

Shagreen patch or plaque: These are raised flat plaques of varying sizes, from a few millimeters to 1 or 2 cm. in diameter, found on the face,

Fig. 2.—Case 2. The red seedlike type of adenoma sebaceum.

lumbar region, or the trunk. The surface usually shows horizontal wrinkling. The color is the same as the skin. The lesions may be discrete or coalesce to form large patches which are highly characteristic of tuberous sclerosis.[31] Several of our patients have these plaques. Indeed, Case 4 was born with these lesions, but their significance was not at first recognized (Fig. 3).

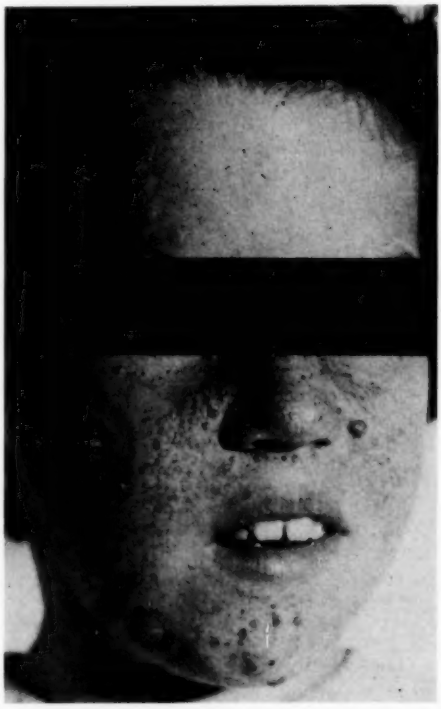

Fig. 3.—Case 4. Nodular type of adenoma sebaceum on cheek and chin and shagreen patch over forehead. (Picture courtesy of Dr. R. O. Brauer, Houston, Texas.)

Subungual fibromas: These lesions, which are also peculiar to tuberous sclerosis,[31] are firm, flesh-colored growths, emerging from the groove of the nail bed to lie on the nail plate. They often appear during or after adolescence. The patient in case 7 came to the clinic in status epilepticus at 15 years of age. The presence of subungual fibroma immediately suggested the diagnosis.

Café au lait spots and others: Oval or circular areas of brown pigment may be scattered over the trunk and the limbs. Their size and number vary considerably. Other lesions such as depigmented patches (areas of vitiligo) may be present; they have been more common than café au lait spots in tuberous sclerosis in our series. Neither of these skin changes is specifically diagnostic (Fig. 4).

Two patients in this series have hairless spots over the scalp. They were apparently born with this defect.

Dermal tags and warty, flat xanthomatous spots or patches have been described and have been observed among our patients.

Retinal Changes.—Grayish or yellowish granular areas may be seen in the retina. Among our patients, Case 8 presented a glistening whitish patch about the size of an optic disc in the left retina.

LABORATORY DATA

Radiographic Findings.—Roentgenographic examination of the skull may reveal abnormal intracranial calcification.[32] These calcium deposits are small, discrete, and irregularly scattered and are most often found in the region of the basal ganglia. Three patients in our series exhibited this finding (Fig. 5).

Calcified areas and general thickening in the calvarium may be seen.[16] Two of our older patients (Cases 2 and 7) had thickened calvariums.

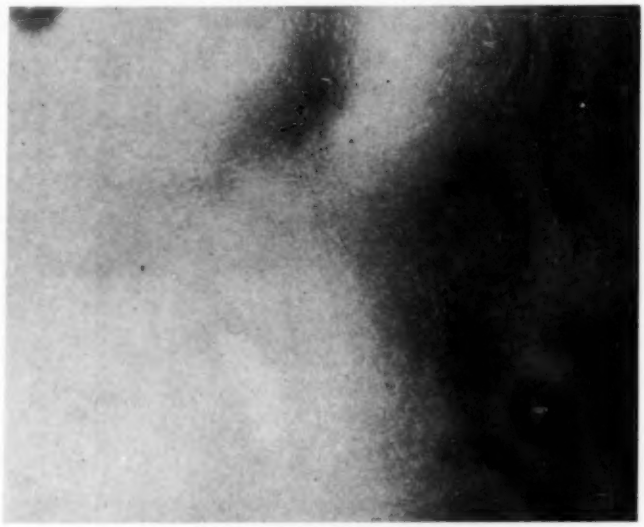

Fig. 4.—Case 1. Depigmented and pigmented areas of skin over chest.

Family History.—The family history is surprisingly negative for neurocutaneous syndromes in our group of patients. In only one instance, Case 1, was there a positive family incidence: the father having the subcutaneous nodular type of neurofibromatosis and a younger brother having a few café au lait spots on the body and a small cavernous hemangioma on the shoulder.

Other reported changes such as periosteal thickening and cystic changes of the metacarpal and metatarsal bones,[24, 33] have not been found in the skeletal surveys of our patients. However, generalized osteoporosis was found in Case 2.

Pneumoencephalography.—This examination may reveal "potato-like" masses projecting into the ventricles,

TABLE V. LABORATORY DATA

CASE	ROENTGENOGRAM OF SKULL	PNEUMOENCEPHALOGRAM	ELECTRO-CARDIO-GRAM	INTRA-VENOUS PYELO-GRAM	SKELETAL SURVEY
1	Negative	Dilatation of ventricles, bulbous mass in ventricles	Negative	Negative	Negative
2	Thick calvarium	Moderately dilated ventricles, no definite nodules	Negative	Negative	Generalized osteoporosis
3	Negative	Not done	Not done	Not done	Not done
4	Negative	Not done	Not done	Not done	Negative
5	Negative	Negative	Negative	Negative	Negative
6	Intracranial calcification	Dilatation of ventricular system, tenting and suggestive nodules of ventricular wall	Negative	Negative	Negative
7	Intracranial calcification and thick calvarium	Dilatation of ventricles	Negative	Negative	Not done
8	Intracranial calcification	Dilatation of ventricular system, nodular masses in ventricles	Not done	Not done	Not done

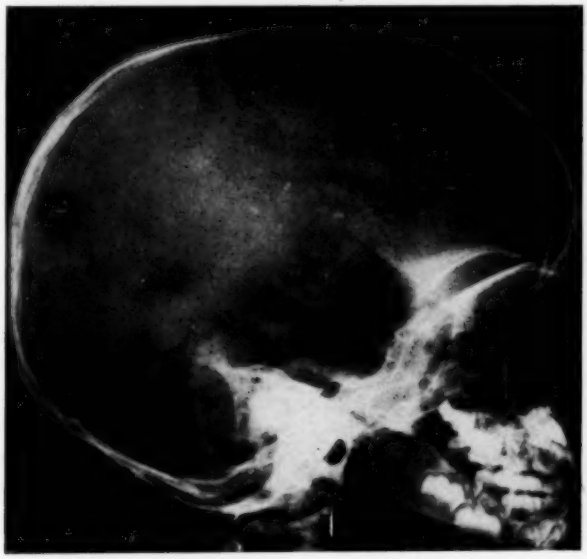

Fig. 5.—Case 6. Intracranial calcification in region of basal ganglia.

with resultant distortion and dilatation. This finding is peculiar to tuberous sclerosis and is a pathognomonic sign of this disease.[34] This examination was carried out in 6 of our 8 patients. In 2 patients (Cases 1, 6, and 8) nodular projections into the ventricles were demonstrated (Fig. 6).

Electroencephalography.—The electroencephalographic findings in our group were very abnormal and strikingly consistent; the younger the patient, the more abnormal was the electroencephalogram (Table II). The tracings in the younger group show continuous slow spike-wave activity of the type shown in Fig. 1,

with or without additional focal activity. The electroencephalographic pattern often showed changes with increasing age. For example, in Case 2, at 2 years of age, abnormal continuous slow spike-wave activity was associated with massive spasms and akinetic seizures (Fig. 1). At 10 3/12 years of age, the tracings showed poor regulation and poor organization with paroxysmal slow activity (Fig. 7). At this time the patient had only very infrequent right-sided focal motor seizures.

Other Laboratory Findings.—Abnormal electrocardiographic and pyelographic changes have been reported in patients in whom there was cardiac and renal involvement. These are usually complications of later life and are rare in children. None of our patients in whom these tests were made showed such abnormalities.

DIAGNOSIS

The diagnosis of tuberous sclerosis is easy when all features of the triad are present. In the absence of the

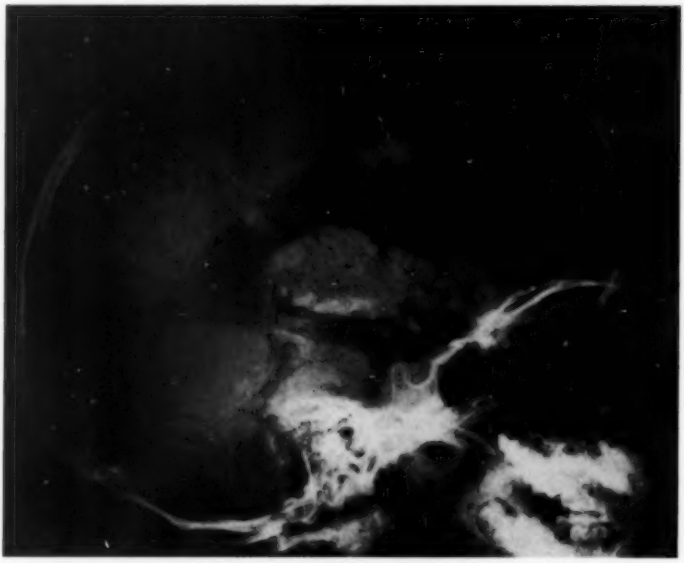

Fig. 6.—Case 1. Pneumoencephalogram of dilatation of ventricular system with "candle guttering" masses.

TABLE VI. OTHER ABNORMALITIES

CASE	HEAD SIZE	EPICANTHAL FOLDS	HIGH-ARCHED PALATE	TRUNK	LIMBS AND OTHER
1	Large	–	–	–	–
2	Large	+	++	–	Short fifth fingers
3	Large	–	–	–	Spade-handed
4	Normal	+	+	–	Short fifth fingers
5	Small	–	+	–	–
6	Small	–	–	Sacrococcygeal dimple	–
7	Normal	–	–	–	–
8	Small	–	–	+	Ears not equal

characteristic facial lesions the diagnosis is more difficult; this is frequently the case in infants. However, the presence of cutaneous changes other than adenoma sebaceum in association with protracted seizures and delayed development is highly suggestive of this syndrome.

anomalies or by evidence of disturbed cerebral function. Table VI presents coexisting developmental stigmata among our patients.

MANAGEMENT

Tuberous sclerosis is a social as well as a medical problem. The manage-

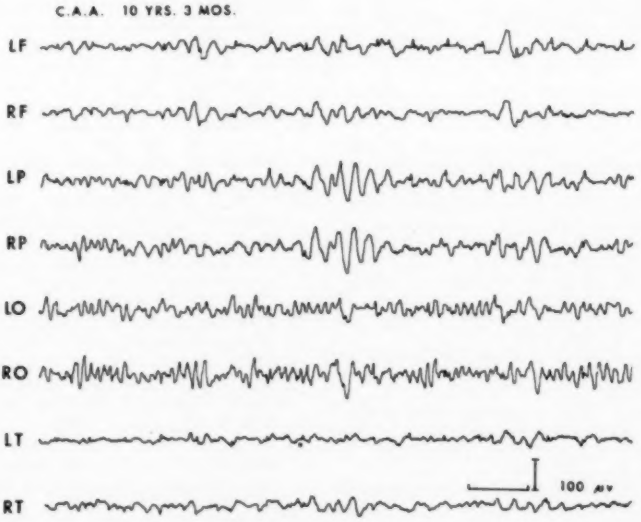

Fig. 7.—Case 2. Electroencephalogram of patient at 10 3/12 years of age showing poor regulation and organization, with paroxysmal slow activity.

When there are no clinical signs other than seizures, the diagnosis of tuberous sclerosis during life is practically impossible, except when the characteristic roentgenographic findings are demonstrated. In other incomplete forms, which are probably more common in infants, the diagnosis of tuberous sclerosis can often be made only at postmortem examination.[35, 36, 37] It should be recognized that adenoma sebaceum may be present without mental defect.[12, 38]

The diagnosis may be facilitated by the presence of other structural

ment of the patient should be individualized in accordance with the mental and behavioral changes, the severity of seizures, and the circumstances of the family. Patients with the mild form may make an adequate social adjustment and be cared for at home. Marked mental deficiency may necessitate custodial care. The treatment of seizures with anticonvulsant drugs is often only partially effective. Spiegel, Wycis, and Baird have recently reported 2 patients with tuberous sclerosis whose seizures were treated by electrolytic pallidotomy.[28, 39]

PROGNOSIS

The fully affected patient rarely lives more than 25 years[15]; the expectancy of life depends on the location and extent of the disease in the central nervous system. Status epilepticus or intercurrent disease is often the immediate cause of death. Cardiac and renal involvement has occasionally been responsible for death in adults but has not been reported in children.

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"While others, not without reason, are calling loudly for improvements in dwellings of the poor, and for other measures urgently demanded by the increasing population of our towns, I would contend the right management of infants and children lies at the root of all other plans of social amelioration. What can good subsequent measures avail, for a constitution already hopelessly injured by errors in the opening of life?

"'Just as a twig is bent, the tree's inclined.'"

Quoted from book entitled "On the Hygienic Management of Infants and Children," by T. Herbert Barker, M.D. From the British Medical Journal, June 25, 1859.

THE HEART IN PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

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THE finding of a specific muscular lesion in the hearts of patients with progressive pseudohypertrophic muscular dystrophy (P.M.D.) is much more common than one is led to believe from reading the standard textbooks or journals. It is customary to think of this disease as one of the skeletal muscle alone and to relegate the cardiac involvement to a position of minor importance or even of pathologic curiosity.

The study of two brothers with P.M.D., in a family in which 4 male siblings with this disease have died with severe cardiac involvement and 2 living siblings with this disease have evidence of heart disease has prompted this report and review of the literature.

CASE REPORTS

CASE 1.—(Sinai Hospital No. 151-137) (14 in Fig. 1). K. J., a 12-year-old Negro boy, was admitted to Sinai Hospital on Sept. 6, 1957, for biochemical investigation relating to the administration of tocopherol in cases of progressive muscular dystrophy. He was thought to be entirely well until March 16, 1957, when he became feverish, nauseated, and anoretic; these symptoms were followed shortly by dyspnea, cough, and edema of the lower extremities.

He was admitted to the Peninsula General Hospital on April 15. Physical examination at that time revealed the patient to be dyspneic, with a pulse rate of 120 per minute and with pitting edema of the lower extremities. Laboratory examinations showed a leukocytosis, albuminuria, and a blood urea of 13.0 mg. per cent. A diagnosis of progressive muscular dystrophy with possible endocardial fibroelastosis was made. He was given digitalis and was discharged as improved on May 9 on limited activity and maintenance therapy with Digoxin.

One month later he again became edematous and developed a "one-pillow" orthopnea. On June 20 he was admitted to the Harriet Lane Home of the Johns Hopkins Hospital for cardiac evaluation. On physical examination he was found to be a weak but apparently well-nourished boy with typical findings of severe progressive pseudohypertrophic muscular dystrophy with marked cardiac enlargement and congestive cardiac failure. The cardiac condition improved on a low-salt diet and digitalis, but generally his condition remained poor. Intravenous administration of tocopherol polyethylene glycol succinate, 50 mg. twice a week for four weeks, was tried but had no noticeable effect either clinically or on the urinary creatine and creatinine excretion, blood aldolase, or transaminase levels (Table I). He was discharged in August 6 on Digalen, 50 mg. daily, low-salt diet, and bed rest. At home he

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Presented before the Pediatric Section, Baltimore City Medical Society Meeting, March 11, 1958.

This study was supported by The Muscular Dystrophy Associations of America, Inc.

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TABLE I. SUMMARY OF BIOCHEMICAL STUDIES OF FAMILY J

PATIENT	CODE NUMBER ON PEDIGREE CHART	STATUS IN FAMILY	CLINICAL EVIDENCE OF P.M.D.	DATE	SERUM ALDOLASE* (UNITS)	SERUM GLUTAMIC OXALIC-ACETIC TRANSAMINASE* (UNITS)	SERUM TOCOPHEROL* (MG. PER CENT)	REMARKS
E. J.	1	Mother	No	7/10/57	6	18	0.71	
E. C.	2	Sister	No	7/24/57	3	24	0.81	
M. M.	3	Sister	No	7/24/57	11	24	0.70	
G. J.	6	Sister	No	7/24/57	16	22	0.75	
C. J.	12	Brother	No	7/10/57	7	15	0.52	
P. J.	11	Brother	Yes	7/10/57	40	38	0.41	Severe case of P.M.D.
G. J.	15	Brother	Yes	7/10/57	71-220	74-120	0.31	Early case of P.M.D.
K. J.	14	Brother	Yes	7/ 5/57	56	40	0.67	Before tocopherol therapy
				8/ 2/57	70	34	0.62	After 4 weeks of intravenous tocopherol therapy
				9/ 6/57	55	61	0.57	Shortly before death

*Normal values: serum aldolase, <15U.; serum glutamic oxalicacetic transaminase, <40U.; serum tocopherol, adults, 0.84 ± 0.3 mg. per cent; 2-12 years old, 0.73 ± 0.2 mg. per cent.

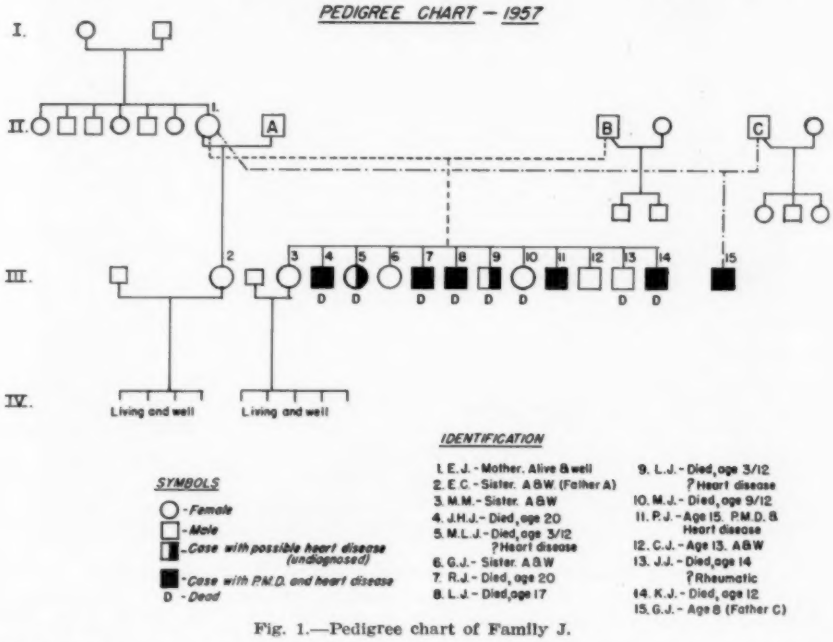

PEDIGREE CHART — 1957
I.
II.
III.
IV.
A
B
C
D
Living and well
Living and well
SYMBOLS
Female
Male
Case with possible heart disease (undiagnosed)
Case with P.M.D. and heart disease
D - Dead
IDENTIFICATION
1. E. J. - Mother. Alive & well
2. E. C. - Sister. A & W. (Father A)
3. M. M. - Sister. A & W
4. J. H. J. - Died, age 20
5. M. L. J. - Died, age 3/12 ? Heart disease
6. G. J. - Sister. A & W
7. R. J. - Died, age 20
8. L. J. - Died, age 17
9. L. J. - Died, age 3/12 ? Heart disease
10. M. J. - Died, age 9/12
11. P. J. - Age 15. P.M.D. & Heart disease
12. C. J. - Age 13. A & W
13. J. J. - Died, age 14 ? Rheumatic
14. K. J. - Died, age 12
15. G. J. - Age 8 (Father C)

Fig. 1.—Pedigree chart of Family J.

had occasional vomiting and tremors.

On Sept. 6, 1957, he was admitted to the Sinai Hospital for continuation of the studies of tocopherol metabolism. Physical examination revealed a morose, lethargic boy with fairly severe and typical pseudohypertrophic muscular dystrophy. There was atrophy of the muscles of the shoulder girdle and marked weakness of the thoracic,

hip, and hamstring muscles. The calf and forearm muscles were markedly enlarged.

The pulse rate was 120 per minute and the respirations, 24 per minute. The precordium was active with a "ripple" over the apical area, but there was no thrill. The heart pulsation was diffuse but the point of maximum intensity was at the anterior axillary line in the fifth intercostal space. The heart sounds were mushy, and P_2 was split. At the apex and transmitted to the axilla was a Grade 2 blowing systolic murmur. The lungs were clear to percussion and auscultation. The liver was 2 cm. below the costal margin, and there was dependent edema.

Therapy for the cardiac decompensation was intensified, but with no effect. On Sept. 25, 1957, he developed a cough with coarse, moist râles at the lung bases which cleared with Gantrisin therapy. Occasionally, he had episodes of vomiting, abdominal pain and distention. On October 2, he manifested acute psychotic phenomena, became violent, and was placed on Sparine. The depression became progressively worse until he refused to eat or speak, and tube feedings were begun. At this time he developed a fever of 102.8° F., cough, and dyspnea, and his lungs were full of diffuse moist râles. He was placed on penicillin, Chloromycetin, and additional digitoxin. Twelve hours later he was found curled at the foot of his bed, screaming, and he died almost immediately.

Laboratory and Special Examinations.—A roentgenogram of the chest on this admission showed marked cardiomegaly, more prominent on the left side. The lung fields were clear (Fig. 2).

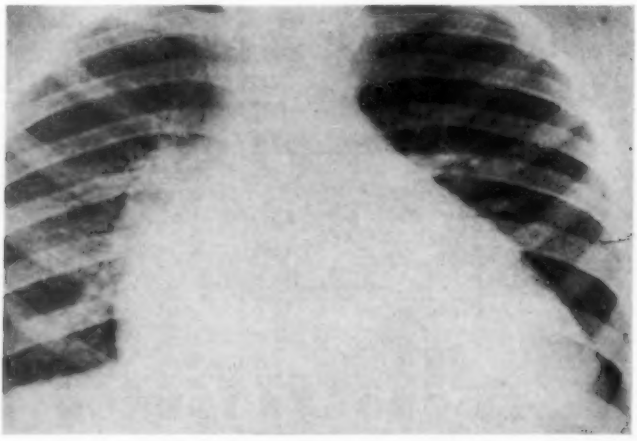


Fig. 2.—X-ray of chest of K. J., which shows generalized cardiac enlargement.

An electrocardiogram showed a heart rate of 150 per minute, sinus rhythm, a P-R interval of 0.14, a QRS duration of 0.08, balanced axis, and semivertical position of the heart. R in V_1 was 5 mm., S in V_1 was 17 mm., R in V_6 was 35 mm., and there were no S waves in V_6. Intrinsicoid deflection in V_1 was 0.02 second and in V_6 0.03 second. There was S-T depression in Leads II, III, aV_R, V_5, and V_6. S-T was elevated in Leads aV_R and aV_L and V_3. The T wave was inverted in V_5 and V_6. There were well-marked Q waves in Lead I, aV_L, V_5, and V_6. The record indicated severe left ventricular hypertrophy and strain compatible

with advanced myocardial disease. Repeated tracings during the hospital stay showed no significant changes.

Blood chemistries and liver function tests were normal. Blood counts were not remarkable and the sedimentation rate was normal. Hemoglobin electrophoresis was normal. The urine was clear.

Urinary creatine and creatinine excretion on a creatine-poor diet showed that 30 per cent of the total creatine and creatinine was excreted as creatine. The blood aldolase varied between 35 and 119 U. (normal is less than 15 U.) and transaminase varied between 34 and 66 U. (normal is less than 40 U.).

The heart was enlarged, weighing 367 grams. All chambers of the heart were dilated and hypertrophied. Areas of grayish-white opaque thickening of the endocardium were present in all chambers of the heart, but particularly in the left ventricle where the opacity was diffuse (Fig. 3). The anterior leaflet of the mitral valve showed a slight diffuse thickening of its substance, with a distinct rolling and thickening of its free margin. The chordae tendineae were thin and inserted normally.

The right pleural cavity contained 150 c.c. of clear, straw-colored fluid and the left one, 100 c.c. of a similar fluid. The lungs were edematous and

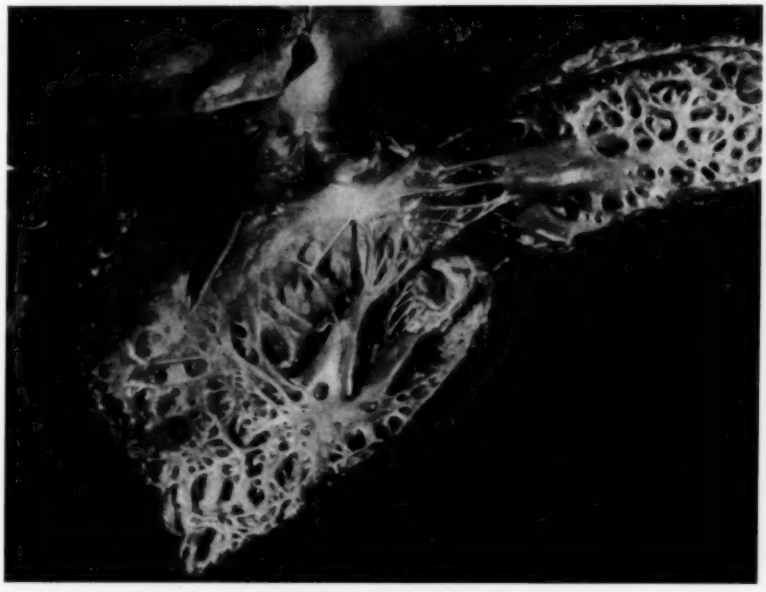


Fig. 3.—Heart; left ventricle showing diffuse endocardial fibroelastosis.

Gross Autopsy Findings.—The pertinent positive findings were as follows: The muscles of the thorax, diaphragm, abdomen, and upper extremities were pale, soft, and thin. The muscles of the back and lower extremities were pale and increased in size.

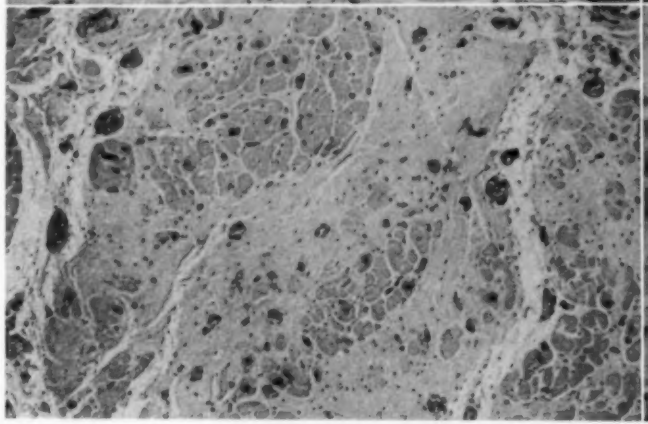
congested. They contained scattered areas of infarction measuring up to 3.0 cm. in diameter. Chronic passive congestion of the liver was evident grossly.

Microscopic Examination.—Sections of the heart taken through the left

Fig. 4A.

Fig. 4B.

Fig. 5.



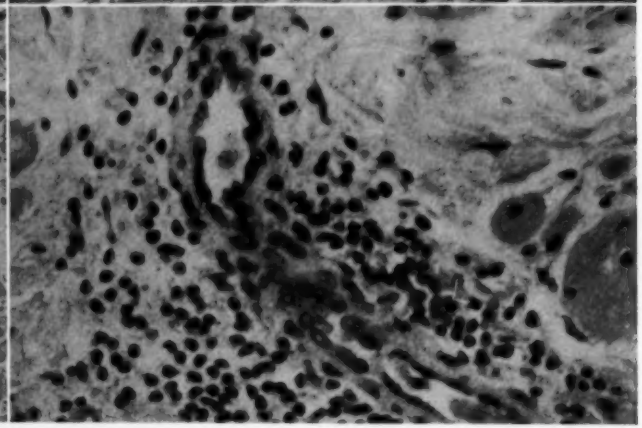


Fig. 6.

Fig. 4.—*A*, Endocardial fibroelastosis. (Hematoxylin and eosin; low power; reduction 1/6.)
B, Endocardial fibroelastosis. Elastica-Von-Giemsa stain showing reduplication of elastic fibers in endocardium. (Low power; reduction 1/6.)
Fig. 5.—Myocardium showing extensive fibrosis. (Low power; reduction 1/6.)
Fig. 6.—Myocardium showing accumulation of lymphocytes in fibrotic area. (High power; reduction 1/6.)

ventricle showed the endocardial thickening to be due to a reduplication of elastic fibers (Figs. 4 and 4*A*). The myocardium immediately adjacent to the endocardium was essentially intact. At some distance from the endocardium and extending as far as the epicardium, the myocardium showed irregular areas of fibrous replacement, with atrophy of muscle fibers and focal accumulations of lymphocytes (Figs. 5 and 6). The fibrous tissue was relatively acellular and contained many vascular channels.

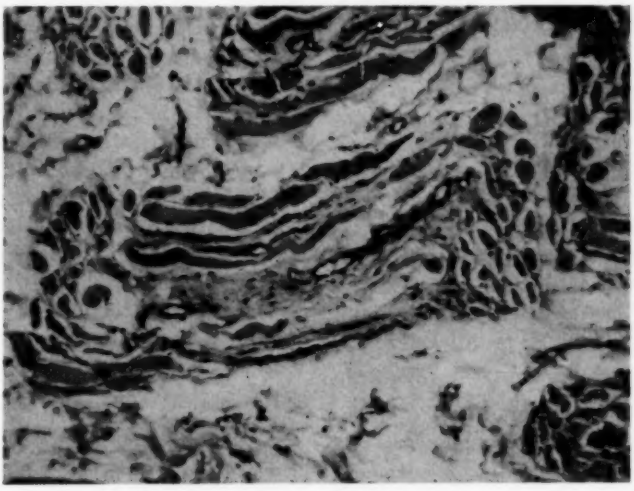


Fig. 7.—Striated muscle showing atrophy of muscle fibers, loss of cross striation, and fibrosis.

Sections of various muscles showed alterations which were essentially similar in all groups. Muscle fibers showed atrophy and loss of cross striations. There were foci of sarcolemic nuclear proliferation and condensation. Focal accumulations of lymphocytes were present. In some areas the endomysium surrounded an empty space devoid of muscle tissue (Fig. 7). In other areas there was some fibrous replacement.

Case 2.—(Sinai Hospital No. 151-138) (15, in Fig. 1). This 8-year-old Negro boy was born of a different father than the other siblings and was admitted on Sept. 6, 1957, to Sinai Hospital for evaluation. According to his mother he was perfectly normal and showed no evidence of P.M.D. While doing special blood studies on members of this family (Table I), we found that the blood aldolase and transaminase of this child was markedly increased, suggesting muscular disease which had not yet become clinically apparent.

On physical examination the patient was found to be a well-nourished boy with lordosis, who had some difficulty on arising from a reclining position. He had the typical findings of mild progressive pseudohypertrophic muscular dystrophy. His heart was not enlarged but there was a Grade 2 systolic murmur at the base. The heart sounds were good.

Roentgenographic examination of the chest showed a normal cardiac silhouette and clear lung fields.

Blood chemistries were normal, with the exception of serum glutamic oxalicacetic transaminase of 120 U. on July 10, 1957, and 71 U. on Sept. 6, 1957, and serum aldolase of 220 U. and 74 U. at these times, respectively. Fasting blood creatine on a creatine-poor

Fig. 6.—Myocardium showing accumulation of lymphocytes in fibrotic area. (High power; reduction 1/6.)

diet was 0.34 mg. per cent and blood creatinine was 0.73 mg. per cent. Sixty-five per cent of the total creatine and creatinine in the urine was being excreted as creatine.

An electrocardiogram showed a heart rate of 75 per minute, regular sinus rhythm, P-R interval of 0.15, and the following abnormalities: fair size Q_1 and Q_2 and $QV_{4,5,6}$ high S-T take-off in Lead V_3, R in V_3 of 22 mm. and greater than S.

This child with evidence of early P.M.D. is under observation and at present has a Grade 2 systolic murmur and an abnormal electrocardiogram as indications of heart involvement. As in the first case, the earliest cardiac sign or symptoms occurred approximately at the same time as the skeletal muscle involvement. It is possible that this child has had evidence of muscular dystrophy for some time, but because of the frequency of these symptoms in this household, the mother may not have noticed it, accepting early muscular weakness and difficulties in rising or climbing stairs as normal phenomena.

ADDITIONAL FAMILY HISTORY

These two cases are of particular interest because the family history shows that P.M.D. with cardiac involvement was present in 4 other male siblings (Fig. 1). J. H. J. (4) was noted to have signs of muscular dystrophy at the age of 10 years, and 9 years later he was found to have severe cardiac disease, after being bedridden for some 3 years. He died in 1948, at the age of 20 years, in cardiac failure, after several episodes of profound shock. Autopsy at Johns Hopkins Hospital revealed involvement of the cardiac muscle in the dystrophic process and the endocardium was diffusely thickened. There were multiple infarcts in various organs which may have accounted for the shocklike attacks. L. J. (8) developed the first signs of P.M.D. at 8 years of age, and cardiac involvement was noted when he was 12 years old. He died some years later in cardiac failure, following episodes of acute distress and shock which resembled those of his older brother, J. H. J., and were probably related to terminal embolic phenomena. Autopsy was refused. R. J. (7) died in 1949, at the age of 20 years, with evidence of severe P.M.D. and heart disease. P. J. (11), who is now 18 years old, was first noted to have P.M.D. at 10 years of age. At this time, there was evidence of mild cardiac involvement. At the age of 15 years the heart was distinctly enlarged, with a systolic murmur, and evidence on the electrocardiogram of progressive myocardial disease and left heart strain. Two other siblings have died at the age of 3 months (5, a girl and 9, a boy) from what the mother thinks was heart disease, and one other male (13) died at 14 years of age from what the mother calls "rheumatic disease."

DISCUSSION

There have been very few reports concerning familial occurrence of cardiac dystrophy. The first report of possible familial involvement is in Nothacker and Letsky's series[1] where 6 of 11 patients with P.M.D. showed myocardial lesions. Among these 6 were 2 brothers with clinical and pathologic evidences of heart disease. Kiloh and Nevin,[2] in 1951, reported on a family of 7 siblings in which one patient, aged 40 years, had progressive muscular dystrophy as well as unexplained cardiomegaly with heart failure. Another died with P.M.D., while a third died with cardiomegaly of undetermined etiology. Two siblings

were alive but with heart disease of unknown etiology and 2 siblings were alive and well. The father and his 3 brothers, as well as the mother, all died with heart disease. The etiology of the cardiac lesions is not explained or proved, but Kiloh and Nevin postulated the occurrence of isolated myocardial involvement as a specific pattern in progressive muscular dystrophy.

So far there has been no study on the mode of transmission of progressive muscular dystrophy with heart involvement. The family reported here shows evidence of a sex-linked recessive gene (Fig. 1). It is of interest that the mother has borne children to 3 different husbands, 2 of whom have fathered male children with P.M.D and cardiac involvement. Also, of 9 male siblings, only one, aged 13 years (12), is alive and well at the time of this report.

Genetic patterns vary in the several clinical types of progressive muscular dystrophy recognized. They may be a sex-linked, simple recessive type or a dominant type. When transmission is through sex-linked or simple recessive factors, the disease is manifested early in life. In contrast, when a dominant mode of inheritance is involved, the onset occurs later in life. Muscular dystrophy accompanied by pseudohypertrophy is usually sex-linked, whereas most cases of fascioscapulohumeral dystrophy appear as a mendelian dominant genetic pattern.[3]

As a whole, there is an important sex predilection for males, the ratio of males to females being about 3 or 4 to 1, and when the condition occurs in females, it is likely to be less severe and less rapidly progressive. In this family there is no evidence, clinical or biochemical, that any of the female siblings are affected.

Clinical.—A few observers have pointed out the frequent occurrence of heart disease in patients with progressive muscular dystrophy. Boas and Lowenberg[4] summarized the work of Meerwein, who studied all the 480 cases of progressive muscular dystrophy reported up to 1904. Of these cases, 89 presented some abnormality of the heart or pulse. He divided these latter patients into 4 groups; Group I consisted of 13 patients with abnormal pulse rates but no cardiac murmurs or evidence of cardiac enlargement; Group II, 12 patients with definite murmurs but no enlargement of the heart; Group III, 49 patients who showed cardiac enlargement; Group IV, 15 autopsied patients who showed definite lesions of the myocardium. With a cardiotachometer, Boas and Lowenberg[4] observed an increased heart rate in addition to extreme lability of the pulse rate in patients with muscular dystrophy. Rubin and Buchberg,[5] in a study of 33 cases of progressive muscular dystrophy, reported specific cardiac muscular changes in 50 per cent of their patients. Clinically, their cardiac cases fell into 3 categories: (1) patients who develop congestive heart failure; (2) patients with arrhythmias or tachycardias; and (3) patients with only ECG manifestations. Weisenfeld and Messinger's[6] analysis of 44 cases at the Bellevue Medical Center, New York, showed that 85 per cent had clinical manifestation of dysfunction of the cardiovascular system. However, in 3 of their 4 cases in

which death was due to cardiac failure, there was little indication of cardiovascular dysfunction until shortly before the terminal episode. The lack of cardiac reserve plays an important role in the terminal course of the disease. Thus, intercurrent pneumonia, which may precipitate cardiac failure, often leads to a rapid and fatal issue.

Some patients may present initially with signs and symptoms of congestive heart failure which interestingly enough often respond to the usual methods of therapy for congestive failure. The 2 patients in this report showed early evidence of cardiac involvement. However, the most common single abnormality which has been observed in about 50 per cent of cases[5] was tachycardia, which occasionally was in the form of paroxysms. Other abnormal cardiac findings as determined by physical or radiologic examination were elicited in 35 per cent of cases, although none of the individual findings occurred with significant frequency. These include disturbances of rhythm, cardiac murmurs, and cardiac enlargement. Roentgenographically, the last is manifested by a generalized hypertrophy of all the chambers. The diagnosis of angina pectoris was made in one patient.[6] Confusing signs and symptoms may result from infarcts in other organs, the emboli arising from either side of the heart. This apparently occurred in 3 of our patients. Cyanosis of the extremities was found in 3 patients[1] with transient episodes of irregularities of cardiac rhythm and no other signs or symptoms of cardiac disease, but, as a cardiac etiological basis for the cyanosis was not definitely established, it was felt to have been part of the generalized trophic changes in the limb musculature.

It is interesting to consider why, if cardiac involvement is so common in this condition, it is not more often recognized clinically. One reason may be that in the late stages of P.M.D. many patients are bedridden and do a minimum of exercise so that exertional dyspnea and easy fatigability as indications of cardiac decompensation are not as evident. Also, some of the signs and symptoms in this disease, such as dyspnea, dependent edema, and cyanosis of the extremities, may be cardiac in origin rather than due to the involvement of the skeletal muscles in the disease process, which is the generally accepted etiological factor.

Electrocardiogram.—Among the abnormal cardiac data recorded, that obtained from the electrocardiogram apparently gave the earliest and most frequent indication of some pathologic change. Eighty per cent of the patients in Weisenfeld and Messinger's[6] series had abnormalities of the electrocardiogram. There is no specific pattern indicative of dystrophic involvement of the heart. Sinus tachycardia is the most frequent finding. Bundle branch block,[7] premature ventricular contractions,[1] and short P-R interval[1] are other findings which may be due to involvement of the conduction system and of the auricular musculature by the specific disease process. T-wave changes are strikingly frequent and may be isoelectric, negative, or diphasic. If enough ventricular musculature is destroyed and replaced, the dystrophic

muscle probably acts from the electrocardiogram viewpoint as dead muscle, and abnormally deep Q waves appear.

In our 2 cases and in 3 of the siblings, electrocardiograms were done, and were found to be abnormal (Table II). In 3 cases these findings were present very early in the disease, probably within months of the onset of skeletal muscular symptoms. The most prominent early changes were an elevated S-T segment in Lead V_3, and deep Q waves in Leads V_5 and V_6. Tall R waves in Leads V_5 and V_6 indicated left heart strain in the majority of these cases. Terminally, the electrocardiographic changes were generalized and nonspecific.

TABLE II. ELECTROCARDIOGRAPHIC ABNORMALITIES IN 5 BROTHERS WITH PROGRESSIVE MUSCULAR DYSTROPHY

PATIENT	AGE	MYOCARDIAL DISEASE	VENTRICULAR STRAIN
K. J. (Case 1)	12	Prominent Q in Lead I; elevated S-T in Lead V_3; deep Q in Leads V_5 and V_6; inverted T in Leads V_5 and V_6	Tall R in Lead V_6; R = 35 mm. (definite left)
G. J. (Case 2)	9	Prominent Q in Leads I and II; elevated S-T in Lead V_3; deep Q in Leads V_5 and V_6	Tall R in Lead V_1; R = 22 mm. (slight right); S = 6 mm.
J. H. J.	19	T_1 and T_2 inverted; deep Q in Lead V_6; inverted T in Leads V_5 and V_6	(? left)
L. J.	12	Prominent Q in Lead I; deep Q in Lead V_3; inverted T in Lead V_5	Tall R in Lead V_5; R = 35 mm. (definite left)
P. J.	10	Elevated S-T segment in Lead V_3; deep Q in Lead V_5	Tall R in Lead V_5 (slight left)
	15	Elevated S-T in Lead V_3; deep Q in Leads V_5 and V_6; Q in Lead I; inverted T in Leads V_5 and V_6	Tall R in Lead V_6; deep S in Lead V_1 (definite left)

Pathologic Findings.—Cardiac muscle does not escape the myopathic process characteristic of progressive muscular dystrophy, evidence that this is a generalized muscular disease involving both the cardiac and voluntary muscular systems. There is a striking similarity in appearance of the lesions in the two types of muscle, although the changes in the heart are usually of a milder degree. In 1908, Bunting[8] found a chronic fibrous myocarditis in a patient presenting the typical picture of muscular dystrophy. The following year, Potter[9] described identical findings in another patient. Goodhart and Globus,[10] in 1918, reported on the changes in the cardiac muscle in 2 cases and, in 1923, Globus[11] recorded a further case in which the myocardium was diseased. Bevans[12] contributed 4 cases in 1945. Another case of fibrosis of the myocardium was found at autopsy in a muscular dystrophic patient in 1947.[7] A review of all the necropsies performed at Montefiore Hospital, New York, from 1911 through 1949 showed 11 cases of progressive muscular dystrophy among 8,843 autopsies, and, of these patients, 6 had dystrophic myocardial lesions resembling those found in striated muscle.[1]

Grossly, the heart may be enlarged[7, 12] or even smaller[11] than normal. There is increased subepicardial adipose tissue,[1, 6, 8, 9, 11, 12] with occasional thickening of the epicardium.[1, 10] The myocardium is pale and flabby, and section of the ventricles reveals irregular patches of translucent or pale gray scars, and coarse muscle fibers. The endocardium may show a slight focal thickening.[6, 8, 12]

On microscopic examination, the epicardium may show increased subepicardial fat which in a few cases[1, 6, 12] seems to invade the myocardium, separating it into groups of muscle bundles. This fatty infiltration is also found in the perivascular areas.

Fibrosis is a prominent feature of the changes in the heart muscle. There are vari-sized areas of scarring which show a tendency to a peculiar distribution.[8, 12] The more extensive lesions are near the epicardial surface where the fibrous tissue which penetrates and replaces the myocardium appears to be continuous with the epicardial fat or thickened epicardium. Their evolution into scars can be traced. In the less affected areas the process apparently involves mainly a proliferation of the perimysium internum without involvement of the perimysium externum, leading to isolation of individual muscle fibers. A large number of small, round fixed connective tissue cells may be seen in the younger advancing scars. The densely scarred older areas are well vascularized by thin-walled blood vessels with small aggregates of fat cells in the scar tissue. In some instances involvement of nerve endings can be demonstrated by special stains. Large areas of hyalinization may be present. Diffuse, but sparse, infiltration of the scar tissue with wandering cells and lymphocytes may be seen, but in the connective tissue trabeculae in the proximity of the blood vessels, there is a greater accumulation of these cells, a feature not unlike the pathologic change in the skeletal muscles. This is presumed to be a reactive phenomenon to the degenerative changes in the neighboring muscle fibers.

The muscle fibers may appear as islands engulfed by scar tissue, the encroaching granulations forming a fringelike appearance. The individual fibers are of varying sizes. There is shrinkage, atrophy with patchy fragmentation, and loss of transverse striations. Some may appear hypertrophied with a large amount of edematous sarcoplasm. There may also be clumping of the cytoplasm. Fat stains may show minute intramuscular fat globules.

The muscle fibers immediately adjacent to the large areas of fibrosis assume an appearance similar to the entrapped fibers. There may be isolated segments of muscle fibers elsewhere in the myocardium undergoing phagocytosis.

The nuclei are involved in the degenerative changes which range from distortion to pyknosis and even actual loss of nuclei. For the most part, they are enlarged, irregular in outline, and unevenly stained. Single muscle fibers may have multiple nuclei.

The papillary muscles in some hearts may show the same thickened, large vacuolated myocardial fibers with hyalinization and edema.[12]

The endocardium may appear slightly thickened, although extensive fibroelastosis, as was seen in Case 1, has been described only by Zatuchni and Aegerter.[13]

The pathogenesis of diffuse endocardial fibroelastosis is controversial. Recent opinions expressed in the literature appear to favor a developmental abnormality the exact nature of which is yet unknown.[14, 15] Weinberg and Himelfarb,[16] who coined the term "endocardial fibroelastosis" in 1943, first reported the disease process in two siblings. Kelly and Andersen[17] suggested that it represents a congenital familial metabolic defect of the myocardium which may be the result of deficiency or abnormality of an enzyme. Anoxia or interference with myocardial circulation has also been considered an adequate cause in other cases.[18-20] Mechanical factors such as increased pressure and abnormal currents of intracardiac blood,[21] infection,[22] and collagen disease[23] have also been postulated as etiological factors. It was not seen in the heart of J. H. J. (4) at autopsy, although the endocardium was reported to be diffusely thickened.

The coronary arteries are not implicated in the disease process, but a few small atheromatous plaques have been described. The valves are not usually involved but the aorta is sometimes hypoplastic.

A nutritional muscular dystrophy resembling the lesions in P.M.D. has been experimentally produced in a variety of species of animals by making them vitamin E deficient.[24, 25] These lesions can be reversed with tocopherol administration. In P.M.D. there is no evidence of vitamin E deficiency, and tocopherol in many forms has been used in this condition without any beneficial results.[26] The patient, Case 1, who was in congestive cardiac failure received intravenous tocopherol polyethylene glycol succinate for one month and its effect on him and particularly on the cardiac status was noted. No appreciable effect clinically, biochemically, or cardiologically was found.

SUMMARY

A study of 2 cases in a family in which 4 male siblings have died with evidence of progressive muscular dystrophy of skeletal and cardiac muscle and in which 2 living male siblings who have this disease also have cardiac involvement is reported. Pathologic study in one case showed evidence of extensive cardiac muscular dystrophy and marked endocardial fibroelastosis. The literature of cardiac involvement in the muscular dystrophic process is reviewed, and the salient clinical and electrocardiographic findings in this condition are noted.

Biochemical studies, including blood glutamic oxalicacetic transaminase and aldolase estimations, showed no difference in this group of cases as compared to those cases with skeletal muscle involvement alone. Intravenous tocopherol polyethylene glycol succinate given to one patient had no effect clinically, biochemically, or cardiologically.

The high incidence of cardiac involvement in P.M.D. is stressed, and it is felt that more attention should be given to the management of the cardiac status in the treatment of these patients.

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STAPHYLOCOCCAL PNEUMONIA IN CHILDREN

A Review of 83 Cases

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PRIMARY staphylococcal pneumonia is a severe bacterial infection, characterized by toxicity, empyema, pneumothorax, and multiple pulmonary abscesses. The disease, as an entity, was first described by Chickering and Park[1] in 1919, during the pandemic of influenza. They reported 153 cases in adults and stressed the virulence of the organism in these infections. Mortality in their series was over 50 per cent, compared with only 10 to 15 per cent for all other types of pneumonia. Since this original report, others have appeared in the medical literature.[2-12] Forbes[13] was the first to call attention to the association between staphylococcal pneumonia and pneumothorax. In his 42 cases slightly over 40 per cent developed this complication.

The mortality rate has always been high, especially among the very young.[14, 15] The advent of sulfonamides and penicillin sharply reduced the mortality rate;[12, 16-19] however, the recent development of resistance to these drugs has created a difficult problem in management.[20] A striking increase of staphylococcal pneumonia was noted during 1956, 1957, and 1958, at the Los Angeles Childrens Hospital, coincident with a sixfold increase in other staphylococcal infections.[20]

The purpose of this report is to review the records of all patients with staphylococcal pneumonia, admitted to this hospital from 1944 to 1958, in order to evaluate the efficacy of newer antibiotics used for therapy.

MATERIAL

Pneumonia due to *Micrococcus (Staphylococcus) pyogenes* var. *aureus* was diagnosed in 83 patients admitted to the hospital during the above period of time. The diagnosis was based on clinical and roentgenographic evidence of pneumonia, associated with either pyopneumothorax or the isolation of the organism from blood or empyema fluid. Cases of pneumonia with only nasopharyngeal cultures yielding staphylococci, but without either pneumothorax or empyema, were excluded from this study.

CLINICAL AND LABORATORY DATA

Fig. 1 shows the yearly incidence in our hospital. Nearly all of these patients have been seen since 1956, emphasizing the increased occurrence of this disease in our community. Ten children developed their pneumonia as

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a complication while hospitalized for other reasons. Two siblings were affected in each of 3 families; 3 patients were children of physicians; 10 had known staphylococcal infection in one of the 10 deaths occurred in infants less than 4 months of age (Fig. 2).

Upper respiratory infections, characterized by nasal discharge, cough,

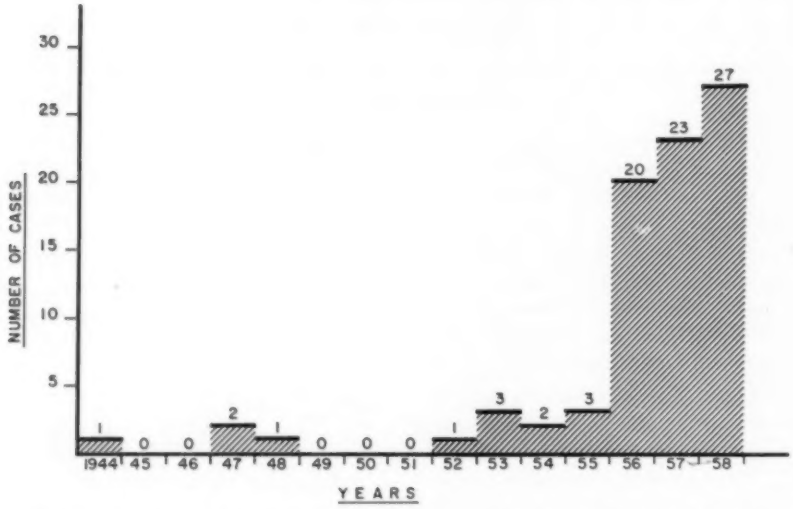

Fig. 1.—Yearly incidence of patients with staphylococcal pneumonia admitted to the Los Angeles Childrens Hospital from 1944 to 1958.

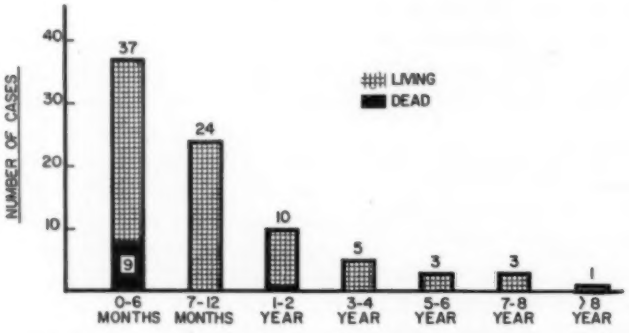

Fig. 2.—Relationship of mortality and age in 83 children with staphylococcal pneumonia.

their families. Measles preceded the onset of pneumonia in 3 patients and chickenpox in one. The age distribution was striking. Sixty-one patients were under 1 year of age, and all but and fever, usually preceded the acute symptoms which brought the child to the hospital. High fever, rapid grunting respirations, and occasionally cyanosis were present on admission.

The majority of the children was treated with sulfonamides or antibiotics prior to admission to the hospital; only 20 were not treated. Usually the physical examination revealed dyspnea, dullness to percussion over the affected lung, and audible râles, with decreased breath sounds on auscultation over the same area.

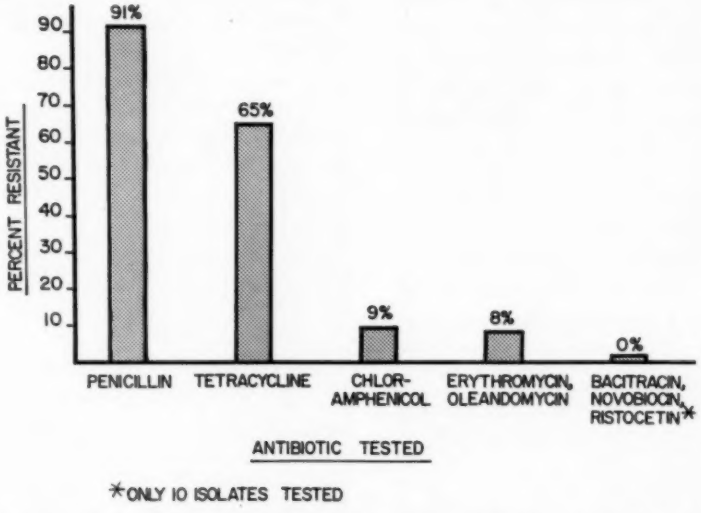

Fig. 3.—Resistance pattern of organisms isolated from 83 children with staphylococcal pneumonia.

There were 10 deaths in this series, a mortality rate of 12 per cent. Associated congenital anomalies were present in 2 of these fatalities. The youngest patient, 10 days of age, died with overwhelming septicemia and empyema; cystic fibrosis of the pancreas was discovered at postmortem examination. The second infant was 22 days of age and had an infantile coaretation of the aorta as well as a bronchogenic cyst and also developed empyema. Seven deaths occurred in very young infants who expired after short illnesses, in spite of antibiotic therapy. There was one fatal postoperative case which was not diagnosed clinically; empyema and multiple abscesses were found at autopsy.

Leukocytosis was commonly present, with moderate granulocytosis. White blood cell counts ranged from 20,000 to 40,000 per cubic millimeter and occasionally as high as 81,000. One infant had a leukopenia of 1,850, with 12 per cent granulocytes; this patient had received chloramphenicol prior to admission.

Nasopharyngeal cultures yielded staphylococci in all but 17 patients. On the other hand, blood cultures were sterile except in 6 patients, 3 of whom were less than 30 days of age. Usually organisms could be isolated from empyema fluid, regardless of the antibiotic therapy used.

Bacterial sensitivity is reviewed in Fig. 3. Nearly all organisms were

resistant to penicillin, and 65 per cent were resistant to tetracycline. None of the isolates tested was found resistant to bacitracin, oleandomycin, novobiocin, or ristocetin, and only 9 and 8 per cent, respectively, showed resistance to chloramphenicol or erythromycin. Appropriate antibiotic selection was important in reducing hospital morbidity. Phage typing was done in 18 patients. All were identified as the "epidemic" strain of staphylococcus phage type 52-42B-81. This organism was uniformly resistant to penicillin and tetracycline.

ROENTGENOGRAPHIC FINDINGS

The chest roentgenograms of every patient showed pneumonia, but only 3 had extensive bilateral disease (Table I). The pneumonia was often

TABLE I. ROENTGENOGRAPHIC FINDINGS IN 83 CHILDREN WITH STAPHYLOCOCCAL PNEUMONIA

Pneumonia	83
Empyema	74
Pneumothorax	42
Cystic changes	48
Abscess	3
Atelectasis	7

lobar in distribution and appeared as a dense homogenous area of infiltration. Occasionally the first study did not demonstrate empyema or pneumothorax, but these sometimes appeared with amazing rapidity. Empyema developed in 74 of 83 patients. Pneumothorax was seen in 42 children, bilaterally in 3. During convalescence, cystic areas appeared in the roentgenograms of 48 patients, generally disappearing in 1 to 2 months. Persistent atelectasis occurred in 7 children and in 3 others there was an abscess in the right middle lobe.

MANAGEMENT, MEDICAL AND SURGICAL

Only 28 of the 83 patients responded to medical therapy alone. Prior to 1955, these patients were usually treated with sulfonamides, penicillin, streptomycin, or tetracycline. The increasing virulence of staphylococcal infection has caused physicians to use at least 2 effective antistaphylococcal drugs and sometimes 3 in desperately ill children. Chloramphenicol and erythromycin were the drugs used in combination most frequently in this series. In combination with other antibiotics, bacitracin was used initially in 24 patients and ristocetin in 7. Bacitracin seemed to be the most effective antibiotic used.

Indications for surgical intervention were pyopneumothorax, failure to respond to medical therapy, persistent atelectasis, and lung abscess. Closed catheter drainage was instituted in all but 4 patients with pyopneumothorax as a routine procedure. Only 2 patients were treated by multiple thoracenteses. Eleven children required decortication of the lung, and 7, rib resection. All 3 patients with lung abscess required lobectomy for cure.

COMPLICATIONS

Generally, complications were few and not serious, except in 2 children who had severe superimposed infection due to pseudomonas bacilli. Nine patients developed severe vomiting and diarrhea while on erythromycin and chloramphenicol therapy. Neutropenia and thrombocytopenia appeared in 4 patients receiving chloramphenicol; they improved when the drug was discontinued. Albuminuria occurred regularly 6 to 10 days after bacitracin therapy was initiated; however, no permanent renal damage was observed.

DISCUSSION

The reasons for the recent increase in the number of serious staphylococcal infections are not yet clear. Evidence is accumulating to substantiate the premise that we are dealing with a more virulent strain of staphylococcus.[21, 22] The epidemic phage strain (52-42B-81) has been responsible for most of the serious outbreaks reported.[23] Of 18 isolates tested in this study, all belonged to this specific phage type. This strain is widely disseminated in our country and is nearly always resistant to penicillin and tetracyline.

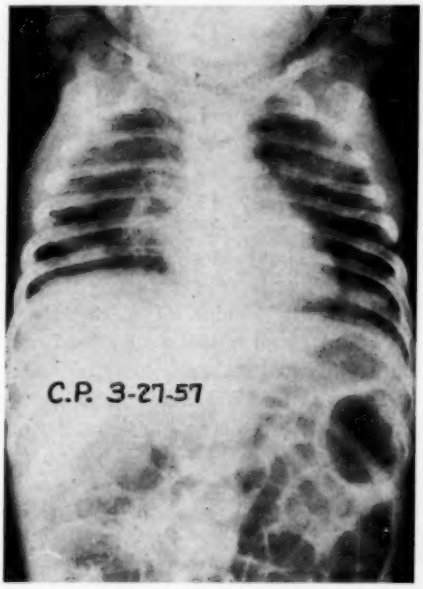

Fig. 4.—Initial chest roentgenograms in a 9-month-old infant with early staphylococcal pneumonia.

It has been proved conclusively that this organism is generally acquired from infants in the newborn nursery, from hospital personnel, or by cross-contamination from other hospitalized patients.[24] Strict aseptic technique in the nurseries may help to prevent outbreaks of this serious infection. All

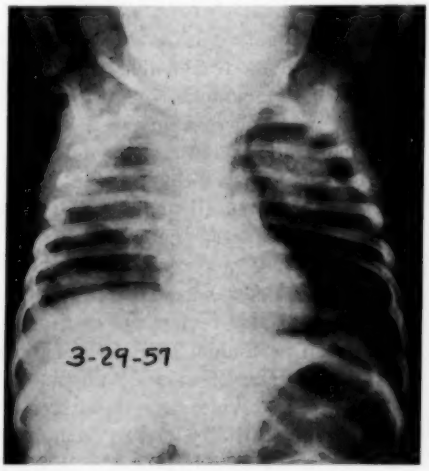

Fig. 5.—Diffuse pneumonic spread and pneumothorax 48 hours after initiation of chloramphenicol therapy.

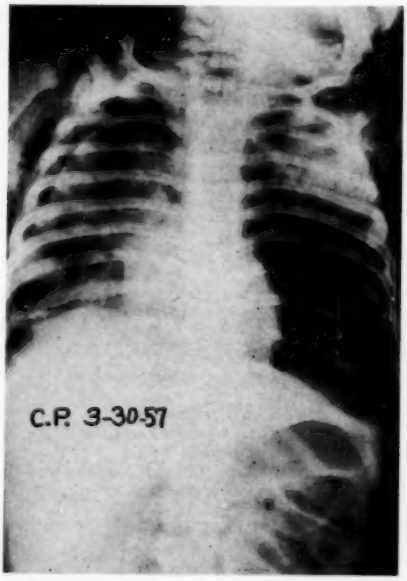

Fig. 6.—Bilateral pyopneumothorax in the same infant as in Fig. 5 just 80 hours after the onset, in spite of intravenous chloramphenicol.

physicians using hospital facilities must be aware of the highly contagious nature of this organism.

The diagnosis of staphylococcal pneumonia is not difficult to make. At present the staphylococcus is the chief etiologic agent responsible for empyema or pyopneumothorax. The latter finding is pathognomonic. A history of furunculosis, measles, or maternal breast abscess should alert the physician to the possibility of this diagnosis in any infant with pneumonia.

The disease may progress rapidly and death may occur within hours. Figs. 4, 5, and 6 review the roentgenograms of a 9-month-old infant who developed staphylococcal pneumonia during his convalescence from severe diarrhea. Initially, lung pathology was quite localized; however, Figs. 5 and 6 demonstrate rapid spread, with bilateral pyopneumothorax developing within 3 days, even though the patient was being treated with 100 mg. of chloramphenicol per kilogram of body weight intravenously.

Our policy has been to use bacitracin with one other antibiotic initially. In severely ill children 3 drugs such as chloramphenicol, oleandomycin, and bacitracin have been used since all are tolerated well parenterally. The dosage of bacitracin used initially was 1,000 U. per kilogram of body weight per day until albuminuria developed in significant amount. The dosage then was reduced to 800 U. per kilogram of body weight per day. If albuminuria persisted, the dosage was further reduced to 600 or 400 U. per kilogram. When it was necessary to continue the drug in spite of albuminuria, blood urea nitrogen determinations were done to help decide when bacitracin was to be discontinued in order to prevent permanent renal damage. The bactericidal action of bacitracin made it a valuable therapeutic agent. Table II shows that patients treated initially with bacitracin usually had a shorter hospital stay and fewer complications than patients treated with other antibiotics. Antibacterial medication was continued for 3 to 6 weeks after patients became afebrile and the chest film showed good clearing.

TABLE II. RELATIONSHIP OF ANTIBACTERIAL THERAPY, AVERAGE HOSPITAL STAY, REQUIRED SURGICAL PROCEDURES, AND MORTALITY IN 83 CHILDREN WITH STAPHYLOCOCCAL PNEUMONIA

YEAR OF ADMISSION	INITIAL ANTIBIOTIC THERAPY	NUMBER OF CASES	DEATHS	AVERAGE HOSPITAL STAY (DAYS)	SURGICAL PROCEDURE			
					NONE	DECORTICATION AND/OR RIB RESECTION	LOBECTOMY	ONLY TUBE DRAINAGE
1944-1955	Penicillin and streptomycin or sulfonamides	7	0	20	4	0	0	3
1955-1956	Penicillin, streptomycin, and tetracycline	18	5	28	3	4	1	5
1956-1957	Chloramphenicol and erythromycin	27	3	28	8	9	2	5
1957-1958	Bacitracin and chloramphenicol and/or oleandomycin	24	2	23	10	3	0	9
1958	Ristocetin and chloramphenicol and/or oleandomycin	7	0	34	3	2	0	2
	Totals	83	10		28	18	3	24

Pyopneumothorax was an indication for immediate closed catheter drainage. Decortication was reserved for patients with persistent atelectasis or poor clinical response. In other patients surgery was withheld since the roentgenogram of the chest often showed remarkable clearing.

SUMMARY

1. The increase in incidence of staphylococcal pneumonia has been pronounced in recent years. The records of 83 patients seen between 1944 and 1958 at the Los Angeles Childrens Hospital are reviewed. Ten patients died, all but one were less than 4 months of age.

2. Bacitracin, chloramphenicol, erythromycin, oleandomycin, and novobiocin were valuable agents for treatment. Bacitracin with one other effective antibiotic resulted in an improved clinical course and a lower mortality rate.

3. Closed catheter drainage was used when empyema or pyopneumothorax occurred. Rib resection was necessary when drainage was inadequate; decortication of the lung was generally reserved for patients with persistent

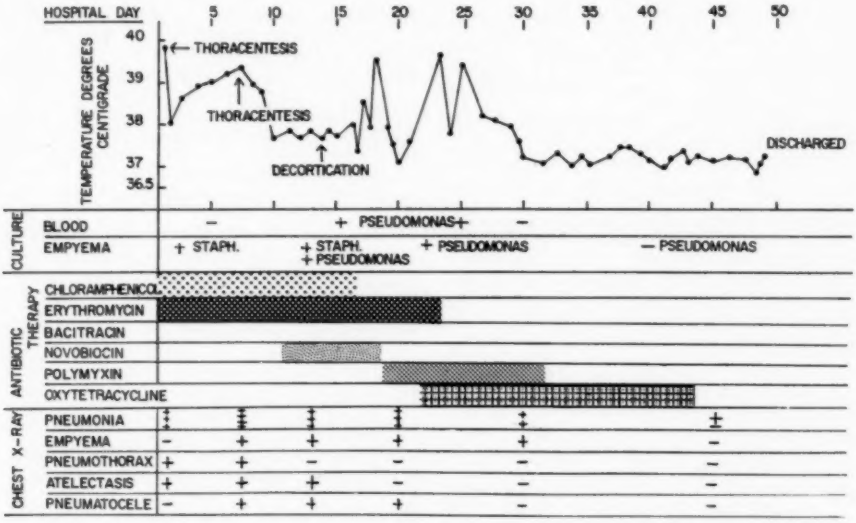

Fig. 7.—The course of an infant with a superinfection due to *Pseudomonas aeruginosa* which occurred during the course of treatment of staphylococcal pneumonia with chloramphenicol, erythromycin, bacitracin, and novobiocin.

The 2 cases of pseudomonas septicemia in this series emphasize the danger of superinfection, which is always present whenever broad-spectrum antibiotics are used. Fig. 7 reviews the clinical course of an infant who developed pseudomonas septicemia following a decortication procedure. He was critically ill for 3 days until specific therapy for pseudomonas was begun. Polymyxin, streptomycin, and oxytetracycline were required for cure. The other infant with pseudomonas septicemia died before adequate treatment was instituted.

atelectasis. Long-continuing pulmonary abscess was seen in the right middle lobe in 3 patients who responded to lobectomy.

4. The danger of superimposed pseudomonas infection is emphasized. Polymyxin with either streptomycin or oxytetracycline is the treatment of choice for this complication.

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STUDIES ON HUMAN LACTATION

Relation Between Dietary Protein and the Various Nitrogenous Constituents of Human Milk

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STUDIES were recently carried out on the effects of the stage of lactation and of the socioeconomic status of the lactating mother on the chemical composition of milk. It was found that the stage of lactation was not a significant variable with regard to fat, protein, and amino acid contents of milk beyond the first month of lactation. Regarding the effect of socioeconomic status, no perceptible differences between the different groups studied could be observed in respect to the carbohydrate content of milk. A significant difference was observed, however, between the very poor and the other groups in regard to the fat content of milk. A tendency for an increase in the protein content of milk of women in higher socioeconomic groups was observed.[1, 2] The observation that there is a tendency for the protein content of milk to increase with socioeconomic status and the fact that the dietary protein intake varies with socioeconomic status led to the present investigations which were aimed at studying more thoroughly the relation between the dietary protein of the lactating mother and the composition of her milk with regard to various nitrogenous constituents. The results are recorded in this paper.

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EXPERIMENTAL

Materials and Methods.—The subjects of this investigation were 60 lactating women of normal health living in and around Baroda. They were in the lactation period of 3 to 4 months.

Collection of Diet and Its Analysis for Protein Content.—Collections were made of equal amounts of all the foodstuffs consumed by the subject per day, including snacks, beverages, and dietary supplements, if any, in the form of vitamins, minerals, etc. After separate weighing of each foodstuff, all the foodstuffs were thoroughly mixed and homogenized. A portion of the homogenized food was dried in an oven at 90° C. for 12 hours. For 3 days separate estimations of the protein content were made by the micro-Kjeldahl method and the average daily intake of protein calculated.

Sampling of Milk for Analysis.—Samples of milk analysis were collected in all cases between two feedings at about 3 P.M. by voluntary expression. The samples were brought to the laboratory in Thermos flasks containing ice powder and were

TABLE I. EFFECT OF THE DIETARY PROTEIN ON THE VARIOUS NITROGENOUS CONSTITUENTS OF HUMAN MILK

CLASSIFICATION OF LACTATING WOMEN	NUMBER OF SUBJECTS INVESTIGATED	MEAN DIETARY INTAKE OF PROTEIN (GRAMS)	NITROGENOUS CONSTITUENTS OF HUMAN MILK EXPRESSED AS GRAMS PER 100 ML.*								
			TOTAL NITROGEN	PROTEIN NITROGEN	NON-PROTEIN NITROGEN	CASEIN NITROGEN	ALBUMIN NITROGEN	GLOBULIN NITROGEN	FREE AMINO ACID NITROGEN	CREATINE NITROGEN	CREATININE NITROGEN
Group I Dietary protein intake 20.0 to 34.3 Gm.	15	26.650	0.1887 ±0.008491	0.1451 ±0.009138	0.04434 ±0.007120	0.09823 ±0.01039	0.03439 ±0.00558	0.01059 ±0.00128	0.03372 ±0.00612	0.007904 ±0.00133	0.002794 ±0.00046
Group II Dietary protein intake 34.3 to 42.8 Gm.	18	39.130	0.2233 ±0.01265	0.1850 ±0.01830	0.03890 ±0.004924	0.1277 ±0.01449	0.03755 ±0.00489	0.01514 ±0.00249	0.01868 ±0.00133	0.009110 ±0.00076	0.002548 ±0.00017
Group III Dietary protein intake 42.8 to 50.0 Gm.	12	48.890	0.2210 ±0.01095	0.1805 ±0.01205	0.03989 ±0.007183	0.1264 ±0.01196	0.03633 ±0.00608	0.01164 ±0.00239	0.02069 ±0.00197	0.008185 ±0.00111	0.0022637 ±0.00035
Group IV Dietary protein intake 50.0 to 75.0 Gm.	15	62.420	0.2257 ±0.01251	0.1821 ±0.01040	0.04554 ±0.005196	0.1279 ±0.00899	0.03767 ±0.00688	0.01377 ±0.00155	0.01838 ±0.00225	0.006631 ±0.00159	0.002549 ±0.00033

*The figures are the mean values with the standard error of the mean.

immediately analyzed. The samples were collected for 3 consecutive days and the average of these trials was taken.

Estimation of the Various Nitrogenous Constituents of Milk.—The total nitrogen content of the milk was estimated by the micro-Kjeldahl method. The nonprotein nitrogen content of milk was estimated according to the method of Folin and Wu.[3] The difference between the total nitrogen content and the nonprotein nitrogen content was taken as the protein nitrogen content of milk.

To estimate the casein nitrogen of milk, the casein was precipitated from milk at pH 4.7 according to the method of Chiba and associates.[4] The precipitate was centrifuged and washed 3 times with distilled water. The washed precipitate was digested with concentrated sulfuric acid and its nitrogen was estimated by the micro-Kjeldahl method.

The filtrate obtained after precipitating casein from milk was used for the estimation of the globulin content of milk. The filtrate was precipitated by saturating it with magnesium sulfate according to the method of Sabelien.[5] The precipitate was removed by centrifugation, digested with concentrated sulfuric acid, and the nitrogen content estimated by the micro-Kjeldahl method.

The filtrate obtained after precipitating globulin from milk was used for the estimation of albumin. It was heated in a boiling water bath for 15 minutes and the albumin precipitated by heat coagulation. The precipitate was centrifuged, digested with concentrated sulfuric acid, and the nitrogen content estimated by the micro-Kjeldahl method.

The free amino acid nitrogen content of milk was estimated on Folin-Wu filtrate according to the method of Danielson.[6] The same filtrate was used to estimate creatine and creatinine contents of milk according to the method of Folin and Wu.[3]

All the values were expressed in terms of grams of nitrogen per 100 ml. of milk sample.

RESULTS AND DISCUSSION

To discover the relationship between dietary protein intake and various nitrogenous constituents of milk, the data were first classified into a frequency distribution with regard to dietary protein intake and the median and the two quartiles determined for the distribution. (The first quartile was 34.3 Gm., the median, 42.8 Gm., and the third quartile, 50.0 Gm.) The subjects were then divided into four groups according to the quartile range in which they fell. The mean value for the various nitrogenous constituents of milk for the subjects in each group was then determined. Table I shows the relation between dietary protein intake and the various nitrogenous constituents of milk.

It is seen from Table I that the increase in dietary intake of protein from Group I to Group II is accompanied by an increase in the total nitrogen and protein nitrogen contents of milk and that increases in dietary protein from Group II onward are not accompanied by similar increases in these constituents, the values being almost the same for Groups II to IV. The difference between Groups I and II is statistically significant with regard to total nitrogen ($t = 2.2722$), whereas with regard to protein nitrogen it falls just short of significance

at the 5 per cent level ($t = 1.953$) but becomes significant when Group I is compared with either Group III ($t = 2.341$) or Group IV ($t = 2.671$). Thus, it would appear that initial increases in protein intake result in an increase in these nitrogenous constituents of milk and that beyond a certain level of protein intake such increases have no apparent effect. Free amino acid nitrogen in milk, on the other hand, is seen to show a significant decrease from Group I to Group II ($t = 2.401$).

No consistent relation appears to exist between dietary protein on the one hand and nonprotein nitrogen, globulin nitrogen, creatine nitrogen, and creatinine nitrogen contents of milk on the other.

SUMMARY

Dietary protein and the various nitrogenous constituents of milk of 60 lactating women were estimated and it was found that intitial increases in dietary protein were accompanied by an increase in the total nitrogen and protein nitrogen contents of milk and a decrease in the free amino acid nitrogen content, a further increase of dietary protein having no effect on the amount of these constituents in milk.

We wish to thank the Indian Council of Medical Research for having sponsored this project, Miss J. Kapur for her help in collecting diet as well as milk samples of lactating women, and Dr. R. Rajalakshmi for her statistical guidance.

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EMOTIONAL FACTORS FAVORING SUCCESSFUL BREAST FEEDING OF INFANTS

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WHILE Ross and Herdan,[1] Naish,[2] Miller,[3] and Barnes and co-workers[4] have considered the physical difficulties encountered during breast feeding, few studies have been done to evaluate the significance of emotional factors which affect milk ejection and production in the human, although the significance of such factors in the human has been alluded to over a long span of centuries, according to Feldman,[5] and has been quite systematically studied in the cow by Peterson and Ludwick,[6] in the rabbit by Cross,[8] and in the sow by Whittlestone.[7] Newton and Newton[9] have demonstrated that the amount of milk obtained by the infant on the fourth post-partum day and subsequent success at breast feeding is significantly related to the mother's positive attitudes about nursing and childbearing. Aside from this study and others of similar nature by Newton and Newton,[10, 11] no systematic attempt has been made to evaluate personality characteristics and emotional factors as they relate to the success or failure of breast feeding.

Three specific questions are considered in this study: (1) Are there significant differences between the personality characteristics of mothers who elect to breast feed and those who elect to bottle feed their infants? (2) What maternal personality characteristics make breast feeding success more likely and less likely? (3) Can the various causes for failure at breast feeding be related to personality factors?

METHODS

The study took place at Parks U. S. Air Force Base Hospital in northern California. Observations were made on 104 consecutively selected mothers who delivered healthy infants from July, 1954, to September, 1954. All were dependents of servicemen, 13 being wives of commissioned officers, 91 wives of enlisted men. Eighty-nine were Caucasian mothers and 15 were non-Caucasian. There were 50 primiparas and 54 multiparas in the group. No attempt was made to promote breast feeding either during the prenatal period or during the lying-in period and no preparations for nursing were advised during pregnancy or prior to the establishment of lactation. A 4-hour feeding schedule was rigidly maintained in the hospital. The average hospital stay was 4 days.

Presented in preliminary form before the Section on Child Psychiatry at a joint meeting of the Western Division of the American Psychiatric Association and the West Coast Psychoanalytic Societies at San Francisco on Oct. 27, 1955.

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The method used for accumulating data on the personality characteristics of the mothers studied consisted of unstructured group interviews during the lying-in period and during well-baby visits. Individual interviews were also used. The observations were made by one individual with training in pediatrics and psychiatry.

On the basis of observations of the mother in the hospital and on the follow-up well-baby visits, a decision was made as to which one of the two contrasting personality characteristics most aptly described her. That is, she would be considered either calm or anxious, motherly or unmotherly, primitive or sophisticated. These particular personality characteristics are defined as follows: ANXIOUS: Two types of maternal anxiety regarding infant care are distinguishable: *Active* and *passive*. The *actively anxious* mother is one who manifests her fear and insecurity in relation to caring for her child by asking numerous questions which reflect her overdetermined concern regarding the well-being, appearance, and care of the infant. The *passively anxious* mother simply looks very perplexed and is clumsy in handling the baby but is unable to express or perhaps understand the difficulty she has in relation to his care. CALM: A relaxed, unself-conscious person who was able to ask questions which reflect undistorted observations of her infant. MOTHERLY: A perceptive, empathic person who easily accepts the responsibility for care of the infant and who shows a willingness and capacity to adapt her own child care practices to meet the infant's physical and emotional needs. Motherly behavior is best thought of in a biological sense, that is, akin to nest building, cuddling, and retrieving in rats and broodiness in hens. UNMOTHERLY: A person who lacks the capacity to relate herself effectively to the care of the infant. In contemporary middle-class American culture this is often manifested by reliance upon rigid and mechanical procedures and overgeneralizations about what infants are like and how their needs should be met. PRIMITIVE: Such a person shows appearance, behavior, and thinking which suggest responsiveness to basic instinctual feelings and identification with less sophisticated elements of society rather than conformity to intellectually and authoritatively elaborated social mores. SOPHISTICATED: Such a person shows behavior, appearance, and thinking which suggest the need to conform to intellectual social conventions and authoritative judgments rather than the need to express basic instinctual feelings (see case illustrations).

RESULTS

The records of the 104 cases were reviewed and tabulated. For the purposes of comparison, the following groups were set up:

I. Mothers whose infants successfully breast fed for a period of 3 weeks or longer (25 or 24 per cent).

II. Mothers whose infants were artificially fed since birth (48 or 46 per cent).

III. Mothers who attempted breast feeding but were unsuccessful due to reasons which have or may have important psychological implications such as ineffective milk ejection, insufficient quantity, difficulty with nipples, or openly expressed psychological problems (25 or 24 per cent).

IV. Mothers who began breast feeding but discontinued due to physical illness without psychological implications in themselves or their infants (6 or 5.5 per cent).

The mean maternal age did not vary significantly between the groups, nor did socioeconomic status as judged by the husbands' rank.

A total of 15 non-Caucasian women were included in this study. Ten of these (67 per cent) elected to breast feed their infants and 8 of these 10 (80 per cent) were successful. Of the 89 Caucasian women in the study, 46 (51 per cent) elected to breast feed and 17 of these 46 (38 per cent) were successful. The non-Caucasian mothers who elected to bottle feed their infants were as a group less primitive and less motherly than those who elected breast feeding. The two non-Caucasian mothers who were unsuccessful at breast feeding were both primiparas. One failed because her husband objected; the other because the infant "wouldn't take the nipple."

Of the 50 primiparas studied, 25 (50 per cent) selected bottle feeding and 25 (50 per cent) selected breast feeding. Of the 54 multiparas studied, 23 (42.6 per cent) selected bottle feeding while 31 (57.4 per cent) selected breast feeding.

Table I shows that the incidence of motherliness was 17 per cent greater in multiparas than it was in primiparas. Calmness occurred 16 per cent more frequently in multiparas than it did in primiparas. Primitiveness occurred only 4 per cent more frequently in multiparas than it did in primiparas. These findings support the commonly accepted notion that multiparas have more confidence and less anxiety in their motherly roles than do primiparas and make mandatory separation of multiparas from primiparas in any study which concerns personality characteristics.

TABLE I

CONTRAST OF PERSONALITY CHARACTERISTICS IN 54 MULTIPARAS & 50 PRIMIPARAS

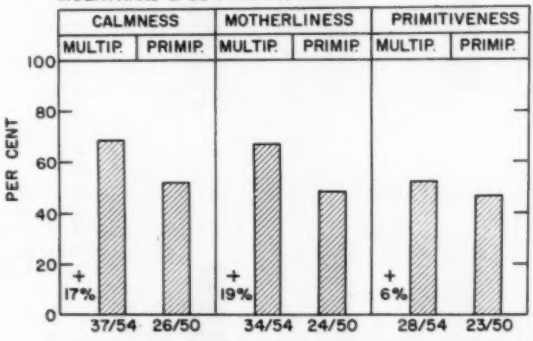


Chart shows that multiparas are significantly more calm and motherly than primiparas.

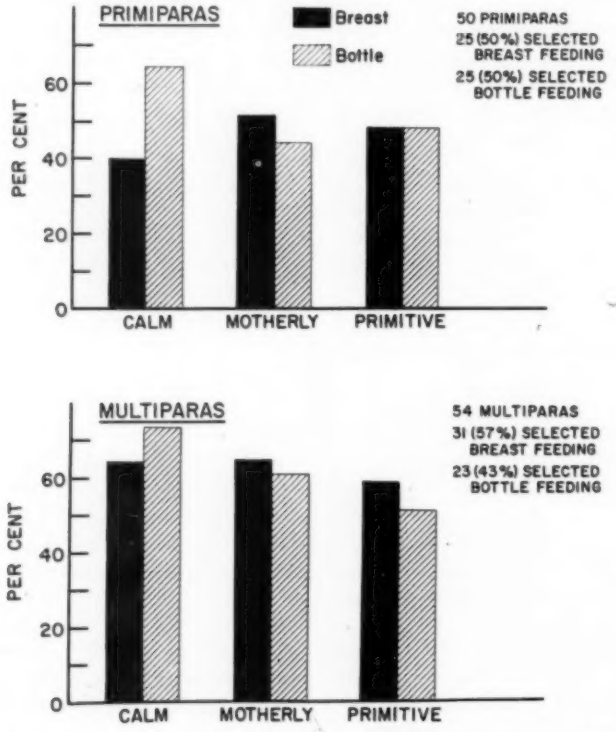
As shown in Table II, the incidence of calmness was 24 per cent less in primiparas who selected breast feeding than it was in primiparas who selected bottle feeding. The incidence of motherliness and primitiveness was about the same in primiparas who selected breast feeding as it was in those who selected bottle feeding. The incidence of motherliness and primitiveness did not differ significantly between the multiparas who selected bottle feeding and those who selected breast feeding.

These findings are important for two reasons. First, it is seen that except for the quality of anxiety, mothers who select breast feeding and those who select bottle feeding do not differ significantly from each other, at least insofar as this study indicates. Second, the fact that both primiparas and multiparas who selected breast feeding were less calm than mothers who selected bottle feeding is interesting, if not immediately explainable.

It will be seen from a breakdown of the data in Table III that the incidence of calmness was essentially the same in primiparas of Group I (60 per cent) and in primiparas of Group II (64 per cent) and that the incidence of calmness in Group I and Group II multiparas was the same (73 per cent), while calmness occurred in only 23 per cent of primiparas of Group III and 58 per cent of multiparas in Group III. Hence, calmness does not seem to distinguish either multiparas or primiparas who will be successful at breast feeding (Group I) from those who select bottle feeding (Group II), but is useful as a criterion to distinguish primiparas who select

TABLE II

INCIDENCE OF PERSONALITY CHARACTERISTICS IN PRIMIPARAS & MULTIPARAS ACCORDING TO CHOICE OF FEEDING.

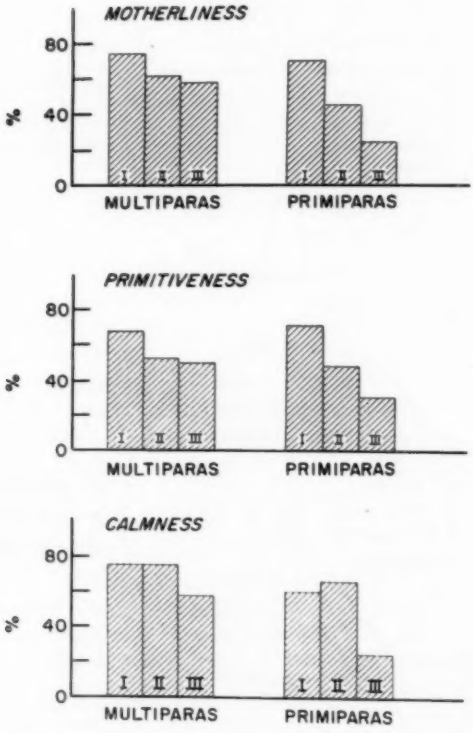


but are unsuccessful at breast feeding (due to reasons with psychological implication) from those who are successful at it.

While motherliness and primitiveness are not adequate criteria to separate mothers who select breast feeding from those who select bottle feeding, Table III shows that these personality characteristics are helpful in distinguishing the mothers who are unsuccessful at breast feeding from those who select bottle feeding and from those who are unsuccessful at breast feeding due to causes which have psychological implications. However, the differences observed between Groups I, II and III in the incidence of primitiveness and motherliness are much greater in primiparas than they are in multiparas and, hence, multiparas are seen to be a more homogenous group, in general, than are primiparas, at least with respect to the personality characteristic of primitiveness and motherliness.

TABLE III

INCIDENCE OF PERSONALITY CHARACTERISTICS ACCORDING TO PARITY & SUBGROUPS I, II & III.



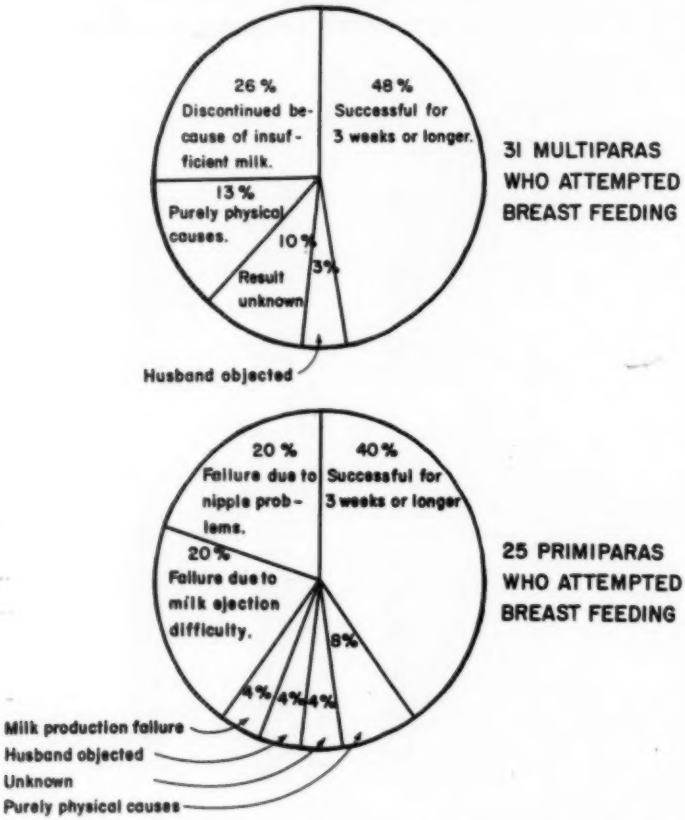
As illustrated in Table IV, of the 31 multiparas who attempted breast feeding, 15 or 48 per cent were successful for 3 weeks or longer. Of the 16 failures, 12 (75 per cent) were due to causes with psychological implications

and 4 (13 per cent) were due to illness in the mother or child without known psychological implications.

In the case of the 25 primiparas, 10 or 40 per cent were successful for 3 weeks or longer. Of the 15 failures, 13 (93 per cent) were due to causes with psychological implications and 2 (7 per cent) were due to illness in the mother or child without known psychological implication.

The reasons for failure of the 12 multiparas and 13 primiparas in Group III are of some interest for comparative purposes. Diminished milk production accounted for 8 failures among the 12 multiparas (75 per cent of failures in Group III multiparas) while 1 case (7.5 per cent of failures) due to diminished milk production was found in the 13 primiparas of Group III. Difficulty with milk ejection (caked breasts, mastitis, and abscess) was found in 5 primiparas or 41 per cent of failures in Group III primiparas, while milk ejection difficulty as a cause of failure was not encountered in the multiparas.

TABLE IV



Nipple difficulty (sore nipples, "could not grasp nipple," cracked nipples) accounted for 5 failures in the primiparas (41 per cent of Group III primipara failures) and none among the multiparas. The husband's objection accounted for failure in 1 primipara and 1 multipara. In 3 multiparas and 1 primipara the cause of failure of breast feeding was not known. In 2 primiparas (4 per cent of 50 primiparas who attempted breast feeding) and 4 multiparas (7.5 per cent of 54 multiparas who attempted breast feeding) breast feeding had to be discontinued due to physical illness in the mother or child without known psychological implication.

From the foregoing data, it is apparent that in the population studied about an equal percentage of multiparas and primiparas attempt to breast feed. Multiparas are slightly more successful at breast feeding (48 per cent as opposed to 40 per cent). In both multiparas and primiparas most failures are due to reasons with psychological implications. However, failure of milk production as a reported cause of failure was much more frequent in multiparas than it was in primiparas, and "caked breasts" and sore, cracked, or "difficult to grasp" nipples as reported causes of failure were much more frequent in primiparas than they were in multiparas.

Why this should be is difficult to answer. These differences may be due in part to a subjective phenomenon. It could be postulated, for example, that primiparas, having experienced breast engorgement and suckling stimulation for the first time, would have some anxiety about these new events and would be relatively more inclined to regard them as painful and caused by "something wrong," and, as a result, discontinue breast feeding. On the other hand, multiparas would, because of their previous experience, regard moderate engorgement and suckling stimulation with less fear, "pain," and little emotional reaction. Another explanation might be that the rigid 4 hour feeding schedule maintained in the hospital was relatively more effective in inhibiting milk ejection in the primipara than in the multipara. The fact remains that excessive engorgement, caked breasts, and mastitis did not occur in the multiparas, and, hence, the physiological mechanisms involving milk ejection must have operated relatively more smoothly in multiparas than in primiparas.

The fact that inadequate milk production was much more frequently the reported cause of failure in multiparas than it was in primiparas would be difficult to explain as a purely subjective phenomenon. Actually, this finding may be more apparent than real and could be explained on the basis that the primiparas who failed at breast feeding due to excessive breast engorgement might have failed due to inadequate milk production had they continued nursing long enough. Until further study is done to control the above variables, it seems safe to say that as a group primiparas are more sensitive than multiparas to psychological actions that inhibit milk ejection. Perhaps the major implication of these findings is the concept that primiparas are more inclined to fail at breast feeding due to factors that impede the smooth operation of the milk ejection reflex, and multiparas are more inclined to fail due to factors that affect the neurohormonal mechanism responsible for milk production.

DISCUSSION

It is conceivable that failure of lactation may be induced by psychological factors in two ways: (1) by inhibiting milk ejection, and (2) by interfering with milk production.

Recently Cross,[8] working with lactating rabbits, has shown that two mechanisms may be involved in the inhibition of milk ejection by emotional factors. The first factor is inhibiting of the neurohormonal mechanisms of the hypothalamus and posterior pituitary, which normally stimulate the production and release of oxytocin. The second factor is hypothalamic stimulation of the sympathetic nervous system which leads to the liberation of vasoconstricting agents from the adrenal medulla which in turn results in constriction of breast blood vessels that, by diminishing blood flow to the breast, diminishes the amount of oxytocin available to stimulate contraction of the myoepithelial cells that actively express milk from the breast acini. Cross's studies on doses of oxytocin required to overcome the latter effects suggest that oxytocin production is more important than breast blood constriction in inhibiting milk ejection by emotional factors.

The way in which milk production may be influenced by nervous and emotional factors is less clearly understood. Initiation of lactation and continuation of lactation in nonlactating female and male rats has been shown to develop from sustained sucking stimulation of the nipple alone.[12] This response can be abolished in rats by denervation of the nipple. The importance of sucking stimulation in the human is attested to by the fact that virgins,[13] grandmothers past the menopause, and women whose breasts had "dried up" following stilbestrol[15] have all produced enough milk to exclusively breast feed infants following a period of a few days to two weeks of preliminary sucking stimulation. This response is most probably mediated by afferent stimuli originating in the nipple being transmitted to the brain stem and hypothalamus and then to the pituitary, with resultant formation of Pitocin from the posterior lobe and prolactin from the anterior lobe. Growth hormone recently has been shown to be very important in milk production[15] and may also be elaborated by such a process.

Newton and Newton[10, 11] have shown that women with positive attitudes about menstruation, pregnancy, childbearing, and nursing are more successful at breast feeding than are women whose attitudes about these biological roles are negative or ambivalent. The current study does show some basic personality characteristics: namely, that unmotherliness, anxiety, and sophistication are more frequently encountered in mothers who have difficulty in milk production than they are in mothers who are successful in breast feeding. The way in which material attitudes, personality characteristics, and emotion may implicate physiological processes controlling milk production remains an unsolved problem in neurohormonal physiology. Both conscious and unconscious factors are probably important and may manifest their influence at a hypothalamic level. That such factors are important in physiological functions such as milk production and ejection should, however, come as no surprise because other hypothalamic-pituitary activities relating to thyroid, adrenal and ovarian function, and physiologic

processes such as gastric secretion and motility, changes in galvanic skin resistance, and blood pressure have been shown to be related sometimes quite crucially to emotional factors, with both conscious and unconscious components.

Although no specific methods were employed to delineate what specific emotional conflicts might be present in women who elected not to nurse or whose lactational difficulty was largely on an emotional basis, the data obtained here and elsewhere are consistent with theoretical consideration of two kinds of conflicts:

1. There is a conflict regarding acceptance of a biological maternal role in relation to the infant versus a role in a society which imposes other conflicting activities and expectations upon women. This kind of conflict probably exists not only in the mothers themselves but also in the general attitudes of middle-class American society.

2. There is the conflict regarding the functioning of the breast itself, that is, as an organ for nourishment of the young versus a sexual organ with the same psychological value in the female as is attributable to the penis in the male. The act of nursing could, therefore, be regarded by some women as a castration threat. Lending support to this concept is the study of Renneker and Cutler[16] who after observing women with breast cancer found that their first and immediate concern was the threat of castration by surgery.

The trend away from breast feeding in this country[17] may be related in part to increased cultural definition of the breast as an exclusively sexual organ in contrast to more "primitive" societies in which the female breast is regarded almost exclusively as an organ for nourishment of the young.[18] One should not make the error of supposing that ours is the first society to have encountered such conflicts. Gellius, a Roman lawyer of the second century, perceived some such prevalent conflict and its implication 1,700 years before Freud when he stated, "Do you believe that kind nature has given women fullness of bosom and beautiful nipples for the purpose of bodily adornment and not for the purpose of feeding their babies?...the natural effect of the child is directed toward that object from which it receives its nourishment and as a consequence a child having no knowledge of its mother does not regret her loss."

SUMMARY AND CONCLUSIONS

A general survey type study, using individuals and group interview techniques in a pediatric setting, was done on 104 consecutive mothers who delivered healthy infants at a U. S. Air Force hospital to determine whether or not significant personality differences existed in those who selected bottle feeding and those who selected breast feeding and if there were personality differences between those who were successful at breast feeding and those who were not. The causes for failure were also analyzed. Specific personality characteristics studied were motherliness, calmness and primitiveness.

1. Forty-six per cent of all the mothers selected bottle feeding (42.6 per cent of multiparas and 50 per cent of primiparas).

2. Forty-eight per cent of multiparas and 40 per cent of primiparas

who selected breast feeding were successful at it for 3 weeks or longer. The most common cause of failure in multiparas was failure of adequate milk production and the most common causes of failure in primiparas were excessive engorgement, caked breasts, mastitis, and sore, cracked, or difficult-to-grasp nipples. It is postulated that primiparas are more sensitive than multiparas to psychological action which inhibits milk ejection. Such would include: (a) rigid 4 hour feeding schedules, (b) subjective pain from initial breast engorgement and sucking stimulation, and (c) hospital routines, professional, and cultural attitudes which discourage the mother from nursing and, as a result, diminish her self-confidence and increase her anxiety.

3. Both primiparas and multiparas who selected to breast feed their infants were slightly more anxious than those who elected to bottle feed. primiparas who were successful at breast feeding were as a group much more calm, motherly, and primitive than primiparas who were unsuccessful. Multiparas who were successful at breast feeding were also more calm, motherly, and primitive than multiparas who were unsuccessful, but the difference between these multipara groups was much less striking than it was between the comparable primipara groups.

4. Ten out of 15 (67 per cent) non-Caucasian women selected breast feeding and 8 of these 10 (80 per cent) were successful at it.

5. The physiology of milk ejection and milk production is reviewed. It is postulated that both conscious and unconscious psychological factors influence milk ejection and milk production via the hypothalamus. On the basis of data here and elsewhere in the literature, two kinds of unconscious psychological conflicts may exist in the mother: conflict regarding acceptance of a biological maternal role and conflict regarding the function of the breast itself, i.e., organ for nourishment of the infant versus sexual organ.

6. It is suggested that the trend away from breast feeding in this country may be related to an increased cultural definition of the breast as an exclusively sexual organ.

7. Even though there are significant psychological differences between the group of mothers who elect breast feeding instead of bottle feeding and between those who are successful at breast feeding and those who are not, it should be emphasized that these differences are not sufficiently reliable to predict success or failure of breast feeding in an individual case. It is the author's opinion that in a large portion of cases the maternal emotional difficulty surrounding breast feeding and infant care is preventable or of a reversible kind and could be effectively dealt with by appropriately timed emotional support during pregnancy, in the hospital, and during the first few weeks following delivery. Critical re-evaluation of hospital routines and professional and cultural attitudes which in this country are generally physiologically and psychologically discouraging to the mother who would like to breast feed is also indicated.

8. Further study on the emotional factors relating to lactation promises to be a fruitful area of investigation.

CASE REPORTS

CASE 1.—This was the first pregnancy for Mrs. T., a 32-year-old white

woman, who had been married for 11 years. Her husband, a 26-year-old major, was stationed "permanently" at Parks Air Force Base, California. The baby was normal. Mrs. T. was seen in a group meeting with 4 other mothers. She was a heavy, powerful-looking woman who wore pancake make-up and freshly applied lipstick. Grooming was extraordinarily meticulous.

She was the first to speak and began by saying, "We have lots of questions." She said that she wanted to breast feed her infant and wondered how to go about it, commenting that the baby didn't seem to like her breast and that he would cry and feed irritably. She complained of sore nipples and axillary pain due to engorged breasts. She asked detailed questions regarding care of the circumcision and the umbilical cord. Five days after delivery the mother had severe "caking" of breasts and breast feeding was discontinued.

Mrs. T. was seen 17 days following delivery with two other mothers in a well-baby clinic, along with their infants. She again looked very well dressed and groomed but quite worried. She undressed the baby awkwardly and then hovered over him during the time he had a stool, wiping off each part of the stool as it emerged from the anus. She asked whether or not the cord was healing properly and was concerned about the eyes, which showed no abnormalities. She stated, "He cries a good deal, has colic, and sucks his fist." It was suggested that she might try using a pacifier with sugar water added and she resisted with the statement that she feared the development of thumb sucking. The two other mothers in the group expressed no great concern or fear of a development of thumb sucking. These comments seemed to reassure Mrs. T. to some extent.

She volunteered the information that she was very tense with this baby but was more so with her adopted 5-year-old boy, explaining that they got him when he was 5 days old and "I was so tense with him. I guess babies are not as fragile as I thought." One of the other mothers reinforced this observation by stating that she had taught all 4 of her other children to swim before the age of 8 months.

Mrs. T. was described as more anxious than calm, more unmotherly than motherly, more sophisticated than primitive. Her comments regarding the baby's difficulty with the breast and the sore nipples were consistent with the idea that breast feeding was a threat to her. Other comments about this infant and her previous infant suggested considerable insecurity and conflict in fulfilling the expectations of a maternal role. The discussion that went on in the group also suggests that Mrs. T.'s difficulties might be considerably alleviated by support from less insecure mothers. Mrs. T.'s failure to successfully breast feed her infant is attributable to failure of physiological operation of the milk ejection reflex and it is postulated that such failure is related to emotional factors.

CASE 2.—This was the third pregnancy for Mrs. L., a 26-year-old white woman, married 11 years to a 30-year-old technical sergeant who was stationed in Korea at the time of Mrs. L.'s delivery. The infant was normal except for a small extra lobe on the right ear.

Mrs. L. was seen with 4 other mothers in a group discussion. She first asked about the "extra tissue" on the ear and accepted without comment the simple reassurance offered her. She then said that she was nursing this infant and had successfully breast fed her 2 other infants. She described her baby as "a little chowhound, quite lazy . . . doesn't want to nurse but just lies back and lets it run in." She said that her first child had died suddenly 4 years ago with blood cancer at 2½ years of age. She indicated that she wanted to breast feed this infant because it's "so close."

Mrs. L. was a small, attractive, well-groomed, and well-dressed woman, with noticeably large breasts. She smiled and laughed easily and was the

most talkative member of the group. She spoke rapidly and at length about the baby, other children, herself, and her husband. Her voluble, pleasant speech and gestures indicated a very "outflowing" person.

Baby L. had obtained 3½ ounces of milk by breast during the largest feeding on the fourth day. Mrs. L. was seen again in the well-baby clinic with two other mothers and their infants 3 weeks later. During the first 3 weeks following discharge from the hospital, he had gained 1.6 pounds. Mrs. L. stated that her baby slept from 9:30 P.M. until 7 A.M. following his third day at home. He ate ravenously during the day but was otherwise calm and no problem. Mrs. L. stated that she lived in a 4-bedroom house with 2 families and 9 children.

She was described as a calm, assured, motherly, "primitive" mother. Because of the unfavorable external circumstances and the death of a young child before this one, one might have expected this mother to have had considerable anxiety and difficulty. That such was not the case suggested that the basic personality and emotional factors are certainly as important or more important than the external stress in influencing milk ejection and production. The contrast between Mrs. L. and Mrs. T., described above, further substantiates this view.

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RESISTANCE TO PSYCHOLOGICAL PROPHYLAXIS IN HOSPITAL PEDIATRICS

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BEVERLY,[1] in a 1936 paper on the effects of illness on emotional development, stated finding only two references[2, 3] on the subject of children's emotional responses to illness, therapeutic procedures, or hospitalization. In 1938, Huschka and Ogden[4] reported that an exhaustive search of the literature for information to help with the specific problem of psychological care in a pediatric outpatient clinic afforded surprisingly disappointing results. They noted an estrangement of the practice of psychiatry from the other branches of medicine. Today, this cannot be considered the case.

The past 2 decades have witnessed a steadily growing interest on the part of mental health and medical workers in the psychological consequences of bodily illness and medical treatment. Attention has been focused on the emotional aspects of various illnesses and handicaps,[5-9] psychological effects of surgery,[10-16] hospitalization, and convalescence.[17-24] Disruptions to the continuity of the young child's relationship with his mother often produce serious developmental effects,[25-32] and such phenomena have been studied as they occur within hospital settings.[33-37] Effort has been directed at empirically assessing the extent and degree of psychological sequelae to hospitalization and operation.[38-44]

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PSYCHOLOGICAL SEQUELAE

A small, but significant, percentage of pediatric hospitalizations involve long stays for young children. In 1951, the World Health Organization published Bowlby's epic monograph, *Maternal Care and Mental Health*,[31] which considered more than 35 papers on the rearing of children within institutional settings. A fund of corroborative reports leaves no doubt on the necessity of adequate psychological management for optimal intellectual and psychosocial development.

It has been emphasized that institutional living need not result in intellectual and behavioral impairment if effort is made to provide a psychologically healthy environment.[45, 46] Evidence has been provided that the frequency of the most severe forms of behavioral impairment stemming from improper institutional conditions may be less than authorities estimate.[47] However, it is not possible on the basis of the literature on this subject[31] to discount expectation of intellectual and psychosocial deficits when prolonged hospitalization occurs in the early years of life under psychologically nonprophylactic conditions. Some children may survive custodial medi-

cal management unscathed; but clearly we must expect undesirable emotional effects persisting to some degree beyond hospitalization[25-27, 29-31, 37]; some children will experience actual and serious impairment of personality and intellect which will characterize relationships to persons and their environment for the entire course of life.[31] It would be illogical to assume that these effects will not occur because of kind intentions on the part of the hospital staff and devotion to the treatment of the medical malady.

The majority of children coming to the hospital do not stay for a very long time. Pediatric experience has shown that brief hospitalization and operative procedures, such as tonsillectomy, often result in unfavorable psychiatric aftereffects when provision is not made for psychological care.

The necessity of psychological prophylaxis for childhood operations and hospitalization becomes evident to persons dealing with emotional disorders. Langford,[48] in 1937, reported a study of 20 children treated psychiatrically for anxiety neurosis. Attacks of anxiety were reported to have had definite etiological relations to previous medical experiences in 7 of 20 cases; 6 of these 7 cases concerned tonsillectomy. Pearson,[10] Deutsch,[49] Edelston,[18] Levy,[11] Miller,[50] Bowlby and associates,[36] Robertson,[51] Gilbert,[52] and others have presented case material on psychological repercussions of hospitalization and operation.

Direct studies of children confirm the observations of many pediatricians[53] that psychological disturbances following brief hospitalization are not isolated occurrences. Jessner and coworkers[39] studied tonsillectomy and reported that 20 per cent of 136 children manifested "severe" postoperative reactions. That such disturbances may not be readily resolved is indicated by Jackson and associates,[38] who studied 105 children hospitalized for tonsillectomy. Seventeen, or 16 per cent, of this group displayed behavioral disturbance 3 months after operation. A concrete system of indexing *overt* behavioral sequelae and a large sample showed approximately 20 per cent of children experiencing prevailing conditions of psychological care to be unfavorably affected 3 months postoperatively (5 per cent when psychologically prophylactic methods were employed).[40]

When there is a greater potential for emotional distress than provided for by tonsillectomy, higher incidences of unfavorable psychological reactions are to be expected. Prugh and associates[41] and Vaughan[43] present evidence on this.

The study by Von Harnack and Oberschelp[44] of 140 hospitalized German children is in important respects confirmatory of other reports in spite of the authors' unusual approach to child psychopathology and conclusions.

PUBLIC HEALTH IMPLICATIONS

The incidence of psychological sequelae to hospitalization reported by researchers[38-41, 43] can be employed to estimate the extent of iatrogenic emotional disturbance in the pediatric population at large. The over-all estimate would be the "incidence level" selected applied to current frequencies of pediatric hospitalization. In that the number of children undergoing tonsillectomy today is estimated to

approach 50 per cent,[54] even the selection of a conservative incidence of psychological sequelae produces astounding yearly estimates of iatrogenic psychological disturbances. We can be sure that many children having sequelae will be able to deal successfully with the emotional forces causing the symptomatic behavior, but we know that for some children the hospital experience has a continuing disruptive effect on development and adjustment.[10, 18, 24, 31, 48-50, 52] Just what percentage of children continue to be disturbed is unknown, but the total number will be considerable even if a very small minority is so affected.

RESISTANCE TO PSYCHOLOGICAL PROPHYLAXIS

The impact of the work of the past 2 decades on children's psychological responses to illness, medical treatment, separation from parents, and hospitalization has resulted in major changes of concepts concerning the psychological care and prophylaxis necessary for babies and children in the hospital. The importance of remedial effort regarding conditions of psychological care of hospitalized children has been stressed by Bakwin,[33-35] Spence,[55] Parry,[56] Powers,[57] Bowlby,[31] Robertson,[24] Stein,[58] and many others.

As a result of the knowledge gained, hospitals have taken steps to institute methods of pediatric care directed at the prevention of psychopathologic sequelae.[45, 59-68]

Nevertheless, the number of hospitals providing adequate psychological prophylaxis to hospitalized children appears to be relatively few.

Efforts aimed at preventing and reducing emotional distress most usually do not pervade the hospital's orientation to the sick child. Modern psychological methods of pediatric management frequently are adopted on a piecemeal basis, brought about by insight and kindness of a few staff members, without reflecting general hospital staff understanding of the mental health issues at stake and the comprehensive effort necessary to prevent psychological distress and damage.[24]

When a child is ill and hospitalized one commonly still finds disregard of humaneness which would be unquestionably provided in other situations. On some pediatric wards one still may witness intermittent crying, over days and sometimes weeks, of babies for their mothers. Pervasive and serious mental reactions induced by medical methods within the framework of young children's isolation from maternal or healthy substitute maternal contact continues to occur and, if it is at all recognized, to be disregarded.

Authorities emphasize the importance of simple and systematic explanations concerning hospitalization pegged at the child's level of comprehension in order to provide reassurance and prevent unnecessary fear and distress. However, it is common experience that this is not always the typical situation in elective admissions.[69]

There are medical experiences such as the repeated injections of young children or isolation for contagious illness which are especially hazardous psychologically. Though physicians often express concern for children in such situations, hospitals and medical groups in the main do not encourage

research for more qualitative understanding of the psychological repercussions and experimental programs for developing alternative methods and prophylactic procedures.

In recent years, the momentum of publication and symposia dealing with mental health aspects of pediatric hospitalization has been considerable. I know of no pediatrician who would argue against reducing distress and unhappiness of hospitalized children to an absolute minimum (if not on a calculated mental health basis then purely as a reflection of professional values and humanitarian ideals). In spite of this unanimity of outlook, hospitals demonstrate a tough resiliency against interpersonal and management practices which, by being aimed at reducing the child's emotional distress and protecting his psychological viability, are instrumental to the successful attainment of institutional objectives and the broad professional goals of pediatric medicine.

A sociomedical *resistance** toward coming to grips with the requirements for effective mental health care of hospitalized children appears to be in effect. Increasing the saturation of articles on iatrogenic emotional distress may not answer this problem adequately.

The hospital milieu resists vigorous action on important mental health and humanitarian aspects of its practice. If we are to prevent hospital-induced psychiatric disturbance in children, we must objectify and clearly formulate the sociomedical factors which impede the development of effective psychological practice in hospital pediatrics. Frank and objective consideration of this resistance to psychological prophylaxis is decidedly within the great tradition, spirit, and objectives of medicine.

Hospitals may wish to employ social scientists for empirical study of the hospital subsociety. Social scientists as experts and outsiders, exploring and participating in institutional activities, are able to formulate social dynamics which are often difficult to perceive by those actively participating within the social subdivision.[70] If handled wisely, no personal threat need be involved. The type of information on hospital social structure and function obtained from such work would complement the contributions of Stanton and Swartz[71] and the papers edited by Greenblatt, Levinson, and Williams[72] concerning other areas of hospital practice, and the papers edited by Merton, Reader, and Kendall[73] on the education of medical students.

Research alone cannot ensure the introduction of prophylactic measures to do away with the iatrogenic psychopathology of pediatric hospitalization. Forthright effort by professional societies promises to be an important means for stimulating attention to this issue. Relying on past cases of major public health problems, the time-tested supervisory techniques of professional organizations, on which our society has come to rely, will probably have to be employed in a far more determinate manner than has been evident to date.

*A term borrowed from the area of individual psychotherapy, employed here to stipulate thwarting of group behavior by group-dynamic factors, e.g., cultural, economic, professional, and administrative influences.

SUMMARY

1. A fund of evidence indicates that improper hospital management often results in psychiatric disturbance.

2. Iatrogenic psychopathology is believed to be a major public health problem.

3. Many hospitals have taken steps to institute psychologically prophylactic management, but the number appears relatively few.

4. Though there is general agreement, either for mental health or humane reasons, on providing adequate psychological care of pediatric patients, hospitals do not develop and institute the necessary management methods for reducing children's fear and emotional distress to an absolute minimum.

5. If iatrogenic psychopathology is to be prevented, it seems necessary to inquire into and formulate the dynamics of the hospital *resistance* to modern psychological management and prophylaxis.

The writer wishes to express his appreciation to Drs. Donal Dunphy, Warren Freiband, John T. Pitkin, and Edmund Shimberg for their reading of this paper and the many helpful suggestions provided. The opinions and assertions in this paper are in no way to be construed as reflecting the views of the above persons nor of the writer's institutional affiliations.

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"Through diet, and through the atmosphere, elements of blood-disorder may enter. Through the former the plasma or fluid, through the latter the corpuscles, are affected. The qualities of the plasma undergo numerous limited changes, from diet, and from various other substances received through the stomach. But it does not follow, necessarily, that the corpuscles must suffer a disturbing change in consequence thereof. They have, up to a certain extent, a property of indifference, non-affinity, or resistance; and therefore maintain their normal constitution and function under various limited alterations of the fluid in which they swim.

"On the other hand from contact of the blood with poisonous substances in the atmosphere, the corpuscles, by reason of the special function of respiration, may be the first part of the blood to suffer disorder; whereupon their disordered condition is reflected upon the plasma, because this fluid is the depository of their excretions. . . ."

Galstonian Lectures on "Fever and Inflammation" delivered before the Royal College of Physicians, London, by William Addison, M.D. From the British Medical Journal, May 7, 1859.

GREATER EFFICIENCY IN OXYGEN THERAPY

An Improved Oxygen Tent

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THE use of oxygen as a therapeutic agent in the treatment of anoxia has been accepted for over 40 years. Many methods and devices have been tried in an effort to achieve maximal therapeutic oxygen levels with a minimum of side effects and discomfort to the patient.

As recently as 1916, intravenous injection of oxygen was attempted.[1] Other unusual modes of oxygen administration such as rectal insufflation,[2] subcutaneous injection,[3] and intravenous hydrogen peroxide[4] are described in the literature. In 1917, Meltzer[5] demonstrated that oropharyngeal insufflation by catheter was effective and, in 1917, Haldane[6] reported favorable results with an oxygen mask. Stadie[2] and Binger[7] developed oxygen chambers which were insulated rooms filled with oxygen. The expense of operating and maintaining such chambers was prohibitive. In 1925, Barach[8] introduced one of the earliest canopies in the form of a hood made of rubberized fabric. Accessory equipment occupied as much space as did the patient's bed. Roth,[9] in 1924, designed an open-bottom hood-type canopy that enclosed the patient's head and shoulders. A partially closed system of oxygen circulation with ice refrigeration was used. Burgess and Burgess,[10] in 1932, introduced the first open-top oxygen box, with modifications in 1934. Batson[11] reported the revival of the Burgess box with the addition of a mist-producing vaporizer bottle and clear Lucite walls.

The four main types of oxygen administration now in general use are nasal catheter, face mask, closed circulatory systems, and some type of enclosure about the patient.

The use of the nasal catheter can produce rapid therapeutic oxygen concentrations (40 to 60 per cent) in the alveoli[12] but the catheter is irritating, the stream of air has a drying effect on the respiratory mucosa, maintenance of proper position of the catheter in the nasopharynx is difficult, and the swallowing of oxygen can be a serious problem. The face mask is used effectively for emergency therapy yet becomes uncomfortable and commonly causes apprehension in the patient. Closed systems are complex, difficult to manage, and probably dangerous without the supervision of a competent anesthesiologist. Most clinicians agree that the best method of oxygen administration for prolonged periods is the canopy enclosure about the patient.

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THEORETICAL AND PRACTICAL CONSIDERATIONS OF OXYGEN THERAPY

The Committee on Public Health Relations of the New York Academy of Medicine[15] recommended for enclosure-type open-bottom oxygen canopies an oxygen concentration of at least 50 volumes per cent, a carbon dioxide concentration of less than 1.5 volumes per cent, 40 to 60 per cent humidity, and a tent temperature of from 15° to 20° C. Refrigeration of the tent is necessary, both for the comfort of the patient and the reduction of cardiac work load, as demonstrated by Burch.[16] He also showed that cooling only one part of the body was as effective in dissipating heat as cooling the whole body. A flow rate of 10 L. per minute is believed necessary to wash out carbon dioxide mechanically and thereby prevent its accumulation.[15]

Since oxygen is heavier than air, it collects at the bottom of an enclosure. Pachman[13] emphasized this fact by pointing out the necessity of minimizing leaks at the bottom of the canopy in order to maintain high oxygen concentrations. Levine[14] states that it is impossible to obtain adequate concentrations of oxygen within the tent if there are rents or tears, or if the patient is too restless to allow adequate tucking of the bottom of the canopy. Patients in the pediatric age group often are not inclined to rest quietly for prolonged periods, especially when anoxia increases restlessness and apprehension. Standard open-bottom canopies cover the head, shoulders, arms, chest, and part of the abdomen. Frequent opening of the tent required in the care of the postoperative or acutely ill patient to gain access to these parts causes loss of oxygen.

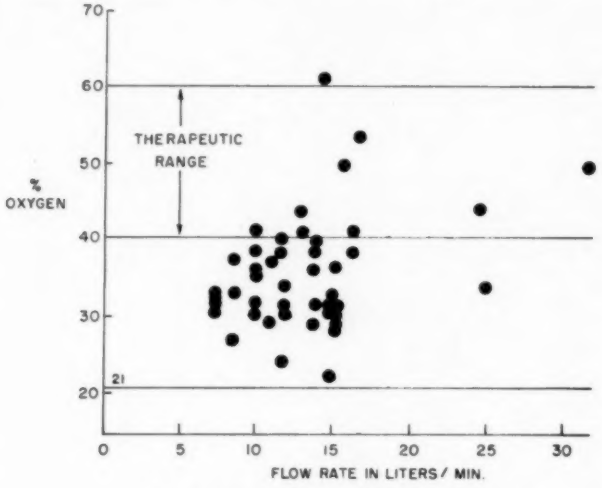

Fig. 1.—Random sampling in standard tents.

Burgess[10] demonstrated that an open top had no effect on oxygen concentration within the Burgess box since the heavier oxygen pools at the bottom. Pachman,[13] however, reported that if

strong convection currents are permitted in the room a "Venturi effect" may tend to pull the oxygen out through the open top of the tent or box.

below 35 volumes per cent (Fig. 1). Similar findings were reported by Batson.[11]

Recognizing these problems, it was felt that a new tent could be devised

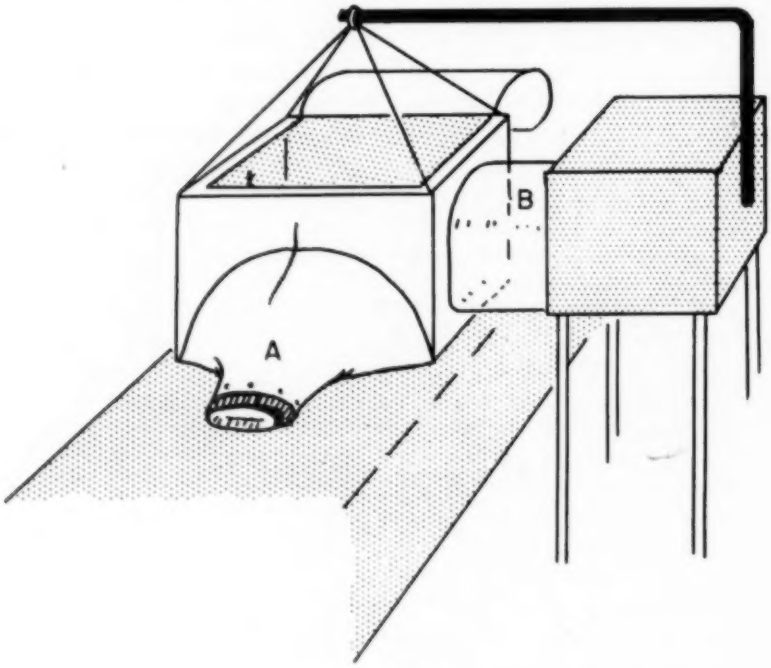

Fig. 2.

The Committee report[15] states, "A flow rate of fifteen liters of oxygen per minute for twenty minutes with a maintenance of ten liters per minute results in an oxygen concentration within the tent of fifty volumes per cent." Our own experience with standard open-bottom canopies in ordinary hospital use, and particularly in the postoperative cardiac patient, has failed to confirm this statement. Random oxygen concentration determinations in 40 oxygen canopies showed that in over one half of the determinations the concentration was

which would ensure constant optimum levels of oxygen concentration and also permit the frequent examinations and procedures required.

DESCRIPTION OF TENT

The tent has an open top, sealed bottom, and is made of transparent plastic fabric. The seams are made airtight by heat sealing. Sleeve *A* (Figs. 2 and 3) projects from the front of the tent, fits around the patient's neck, and then invaginates into the tent proper. A loosely fitting, detachable, stockinette neck piece eliminates the discomfort of

the plastic around the neck. Leakage around the neck piece is negligible. The side sleeve *B* fits over the vent of standard oxygen refrigeration units now in use in most hospitals. Since the top is open, a strong current of air in the room flowing directly over the tent will produce a "Venturi effect" and will reduce the oxygen concentration in the tent. Such currents should be avoided but, if this is impossible, the top may be closed partially with the detachable cover provided for this purpose. A room temperature greater than 80° F. often significantly lowers oxygen concentrations in open-top canopies and the top may be partially closed until room temperature is reduced. A zipper which opens from the top is in the front wall of the tent and provides direct access to the face. The dimensions of the tent proper are 30 by 26 by 24 inches. The oxygen source is the same as that used with any standard refrigeration unit. Either a centrally supplied wall source with reducing gauge and flow meter or commercial oxygen cylinder with gauge and flow meter is satisfactory. A lightweight metal or plastic frame is incorporated in the top border of the tent to maintain its shape. The frame is suspended from the overhead bar attached to most refrigeration units already in use. A tube to be attached to an oxygen analyzer is built into the canopy.

Fig. 3*A*.

Fig. 3*B*.

A nebulizer may be added if needed. The bottom is flexible with no rigid support which allows the patient to be in an upright or supine position. Pillows may be used inside the canopy. Because of the open top, conversation with the patient is easy, and oral medications and nourishment may be given without opening the tent. All procedures involving the chest and abdomen may be performed without disturbing the tent.

COMPARISON OF OPEN-BOTTOM AND SEALED-BOTTOM CANOPIES

Standard open-bottom oxygen canopies and refrigeration units were utilized. Centrally supplied wall oxygen outlets were used with commercial oxygen gauges and flow regulators. Oxygen concentrations were measured with a Mira oxygen analyzer* enabling immediate determinations at frequent intervals. The Mira oxygen analyzer was checked with simultaneous Scholander oxygen determinations and found to be accurate within 3 to 5 per cent. The newly designed tent was found to have carbon dioxide levels consistently less than 1 per cent, as determined by Scholander gas analysis.

Fourteen cardiac patients, who ranged in age from 18 months to 14 years, were treated in the open-bottom canopy. Each of these patients requiring oxygen had rheumatic heart disease or were in the postoperative period following cardiac surgery.

Fig. 4 is derived from studies with an empty open-bottom canopy. It is evident that therapeutic levels are slowly obtained at the commonly used flow rate (14 L. per minute) even without a patient in the tent. Rapid high concentrations are obtained only with very high flow rates (28 L. to 42 L. per minute).

Fig. 5 is a composite curve of oxygen concentrations determined with patients in an open-bottom tent during routine use. The decrease in oxygen concentration with each opening of the tent represents the average decrease as measured in 14 patients treated in this type of tent. Opening the bottom of the tent resulted in a 10 to 20 volumes per cent decrease in oxygen concentration and 10 to 20 minutes was required for the oxygen concentration to return to 40 or 50 volumes per cent. Opening the tent to take a roentgenogram of the chest resulted in an almost immediate reduction of oxygen concentration to room air levels.

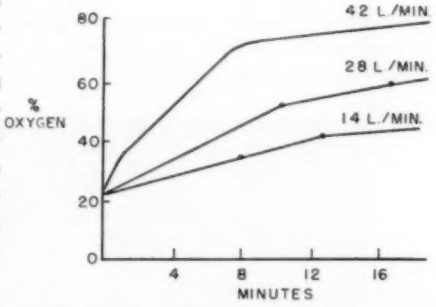

Fig. 4.—Time required to attain therapeutic oxygen concentrations in open-bottom tent. The empty open-bottom canopy was well tucked in around the bottom.

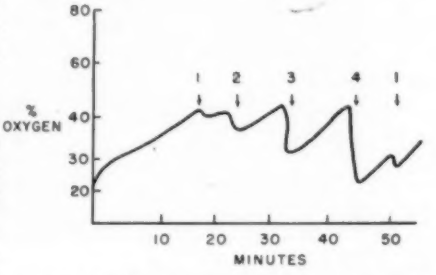

Fig. 5.—Oxygen concentration variations in open-bottom tent. *1*, Zipper opened briefly (2 to 3 per cent drop). *2*, Zipper opened for prolonged period (5 to 8 per cent drop). *3*, Bottom lifted partially (10 to 20 per cent drop). *4*, Bottom lifted completely (> 20 per cent drop).

Fig. 6 compares the rise in oxygen concentration in the empty sealed-bottom tent with the empty open-bottom canopy that has been tucked in to minimize leakage at the bottom. Flow rates of 15 L. per minute were used with

*The Mira oxygen analyzer is manufactured by the Mira Corporation, Los Angeles, Calif. The principle on which it operates is that oxygen will produce a static electric charge on a plate in direct proportion to the concentration of oxygen. A simple galvanometric reading is immediately obtainable.

both. The efficiency of the sealed-bottom tent is clearly demonstrated. Therapeutic oxygen levels were reached within 3½ to 4 minutes in the sealed-bottom tent described here.

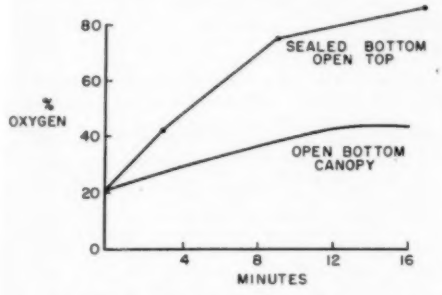

Fig. 6.—Time required to attain therapeutic oxygen levels. A comparison of sealed-bottom open-top tent with tucked-in open-bottom canopy. Both tents were empty and flow rates of 15 L. per minute were used for each.

Fig. 7 demonstrates the fluctuations in oxygen concentration in the open-top sealed-bottom tent. As might be expected, little change in concentration was noted.

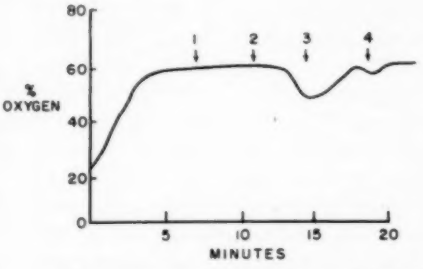

Fig. 7.—Oxygen concentration variations in sealed-bottom tents. *1*, No drop during blood pressure determination. *2*, No drop during x-ray of chest. *3*, Front zipper opened for eating (≅ 10 per cent drop). *4*, Front zipper opened briefly (5 per cent drop).

The temperature within the tent is often different from the temperature recorded on some refrigeration unit thermometers. For this reason we have found it necessary to set the refrigeration unit thermostat on 60° F. to maintain a temperature of 74° F. in the middle portion of the tent.

Subjective reactions are important and have been considered. Patient acceptance has been good. Most of the patients preferred this type of oxygen canopy. The exception was one patient who did not care for any type of tent. The children appeared to be less apprehensive, possibly because the open top allows conversation not hindered by a closed plastic cover.

It is important that the patient be comfortable in any type of tent, but the chief reason for advocating this canopy is to provide adequate, economical, and practical oxygen therapy to the patient in the usual hospital situation.

SUMMARY AND CONCLUSIONS

In our experience the standard open-bottom oxygen canopy in routine hospital use does not provide adequate concentrations of oxygen.

An efficient oxygen canopy is described embodying several well-known principles of oxygen therapy. The essential features of the tent are: a closed bottom to prevent leakage of oxygen, a canopy which covers only the head to permit more frequent examinations and procedures, a smaller canopy which requires less oxygen to obtain optimal concentration, an open top to minimize patient apprehension and allow easy access to the patient's face, and a detachable top which can be employed in the event that strong air currents occur in the room.

In every hospital frequent determinations of oxygen concentrations should be made routinely in all types of canopies to assure the anoxic patient continuous and adequate oxygen.

The canopy described is particularly useful for patients 4 years of age and older, including adults. Patient acceptance has been good.

We wish to express our appreciation to the staff of the Texas Children's Hospital for their interest and cooperation in this endeavor and particularly to Dr. Dan G. McNamara whose support, guidance, and suggestions made our work possible. We are indebted to Dr. Russell J. Blattner and Dr. Denton A. Cooley for their interest and suggestions. Mrs. Marie LaRoza and Miss Lillian Quick of the Housekeeping Department, Texas Children's Hospital, spent many hours making the canopies by hand.

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TREATMENT OF PINE OIL POISONING BY EXCHANGE TRANSFUSION

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EXCHANGE transfusion has been the accepted form of treatment for hyperbilirubinemia in hemolytic disease of the newborn since Mollison and Walker's impressive studies published in 1952.[1] More recently it has been recognized that this procedure is useful in removing toxic substances from the blood and tissues in acute poisonings of children. In 1948, Derot and associates[2] reported the use of exchange transfusion as an adjunct to the successful treatment of sodium chlorate poisoning. Axtrup,[3] in 1950, reported its use in chloramine-T and aniline dye poisonings, advocating it as a last resort if the toxic substance caused blood changes, such as methemoglobinemia. DeCortis and co-workers[4] suggested exchange transfusion in carbon monoxide poisoning. Boggs and Anrode[5] successfully employed this procedure in treatment of boric acid poisoning, as did Kirby in sodium nitrite intoxication.[6] Petit and Herbaut[7] succeeded in lowering the blood level of butazolidin following accidental ingestion by a 15-month-old infant, and Katz and Carver[8] noted dramatic improvement following exchange transfusion in a case of isoniazid poisoning. More commonly, this procedure has been used successfully in treatment of poisoning due to barbiturates,[9] aspirin,[10] and methyl salicylate.[11-12]

Exchange transfusion is a more practical and widely applicable method of removing certain toxins from the body than is hemodialysis by use of the artificial kidney, although hemodialysis is especially useful in acute salicylate and barbiturate intoxication. Abel and associates,[13] in 1913, demonstrated that the artificial kidney could be used to rapidly remove salicylate from the blood of dogs. In 1951, Doolan and co-workers[14] reported the first clinical attempt at hemodialysis in a patient with salicylate intoxication. The patient died, but they were able to obtain a marked reduction in blood salicylate levels with the use of the artificial kidney. In 1955, Schreiner and associates[15] reported the first successful use of hemodialysis in man in salicylate poisoning. Schreiner has since reported its use in a study of 24 patients with dialyzable poisons and 15 patients with nephrotoxic injury.[16] He outlined the principles for selection of poisons to be removed by dialysis and convincingly demonstrated its value in these conditions. He suggested early dialysis to abort the full-blown clinical picture in acute poisonings by dialyzable materials and in nephrotoxic injury.

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Hemodialysis is definitely useful in these types of poisoning, but its widespread use has certain limitations. The necessary equipment is not available in most areas. An experienced team of clinicians and technicians must be available for safe use of the present artificial kidneys. Finally, in infants and very small children, the amount of blood needed to prime the kidney increases the likelihood of either flooding the patient and causing acute congestive heart failure or inducing surgical shock by removing too great a quantity of blood. Most pediatricians have had experience with exchange transfusions. Little special equipment is needed, and in experienced hands, the procedure is usually safe and well tolerated.

CASE REPORT

History.—At 11:45 A.M. on Aug. 30, 1958, a 4-year-old white girl was admitted to the Isolation Ward of Hurley Hospital with a tentative diagnosis of encephalitis. She had been well until the evening prior to admission. Following ingestion of candy, carbonated beverage, and ice cream sundae, she became nauseated and vomited once. She slept well all night, but on the morning of admission she was anorexic and nauseated. At 9:30 A.M., she was given an enema and shortly afterward became listless and lethargic.

Physical Findings.—On admission the girl was acutely ill and comatose. She was a well-developed and fairly well-nourished 4-year-old, weighing 15.9 kilograms. Rectal temperature was 36.8° C.; blood pressure was 80/0 mm. Hg; pulse was 76 per minute and weak; respirations were 24 per minute and shallow. The neck was supple. There was total absence of reflexes, including corneal reflexes, and she was unresponsive to pain. Pupils were of normal size, but did not respond to light. Funduscopic examination was normal. The remaining physical findings were normal.

Laboratory Findings.—The hemoglobin was 14.2 Gm. per 100 ml. and the hematocrit 40 per cent. The white blood count was 10,600 per cubic millimeter, with 83 neutrophils, 1 band cell, 1 eosinophil, 11 lymphocytes, and 4 monocytes. Red cell and platelet morphology was normal. A catheterized urine specimen was clear with an acid reaction, negative for protein and sugar; microscopic examination revealed occasional red blood cells and rare white blood cells per high-power field.

Cerebrospinal fluid examination revealed 2 lymphocytes per cubic millimeter, protein of 16.7 mg. per cent; glucose of 41 mg. per cent; and chloride of 114 mEq. per liter. Culture of cerebrospinal fluid produced no growth.

Blood sugar was 42 mg. per cent; CO_2 capacity was 13.4 mEq. per liter; chloride was 90.4 mEq. per liter; sodium was 132 mEq. per liter; and potassium was 5.4 mEq. per liter.

Initial Course.—Acute poisoning, probably from barbiturates, was felt to be a possibility. Repeated questioning of the girl's mother failed to elicit any evidence of ingestion or administration of potentially toxic substance. Approximately 3 hours after admission, respirations were becoming more shallow and rapid. At this time, the odor of pine oil was detected on the patient's breath. Upon further questioning of her mother, it was found that she had used a commercial disinfectant, Germtrol, in the enema and that the child had never expelled the enema. Two tablespoons of the disinfectant in a pint of water had been used.

The rectum was irrigated with a poor return, and the stomach was lavaged with warm water. The odor of pine oil was present in the rectal contents but not in the return fluid from gastric lavage.

The girl at this time appeared to be in a terminal state. Because of her

deteriorating condition and her complete failure to respond to supportive treatment and intravenous fluids to correct the electrolyte imbalance, an exchange transfusion was decided upon. Estimated blood volume, on the basis of 80 ml. per kilogram of body weight,[17] was 1,280 ml.

Treatment.—Exchange transfusion was started 7 hours after the enema had been given. At the onset of the procedure the patient was deeply comatose, totally areflexic, and completely unresponsive to pain. Respirations were shallow at a rate of 40 per minute, with occasional short periods of apnea necessitating artificial respiration, stimulants, and oxygen. A cutdown was performed on the right saphenofemoral junction, and a polyethylene catheter was inserted into the femoral vein. By means of the push-pull technique, a total of 1,450 ml. of blood was exchanged in 20 ml. increments. One milliliter of 10 per cent calcium gluconate was given after every 100 ml. of blood was exchanged in order to prevent hypocalcemic tetany. Venous pressure remained normal throughout the procedure.

After exchange of 1,100 ml. of blood, corneal reflexes returned. After 1,250 ml. had been exchanged, she began to respond to painful stimulation. The transfusion was performed over a 3 hour and 15 minute period. At the end of the procedure, pulse rate was 140 per minute, respirations were 24 per minute, blood pressure was 140/100 mm. Hg, and rectal temperature was 39° C. Her response to pain was acute enough to require local injection of procaine in order to suture the cutdown site.

Hospital Course.—The girl developed generalized urticaria following the exchange transfusion. This was controlled by intravenous diphenhydramine (Benadryl). One hour post-transfusion, she responded to her name. Vital signs remained stable. Intravenous fluids and oxygen were continued and intramuscular chloramphenicol (Chloromycetin) was started. Four hours after the transfusion she had a good pharyngeal reflex and some return of the deep tendon reflexes. She continued to improve, and the following morning was afebrile, able to answer simple questions, and took oral fluids. Neurologic examination at that time, 12 hours after exchange transfusion, revealed only hypoactive deep tendon reflexes.

Further laboratory examination revealed normal urinalysis. The blood urea nitrogen (BUN) was 17 mg. per cent; CO_2 capacity was 11.6 mEq. per liter; chloride was 97 mEq. per liter; sodium was 133 mEq. per liter, and potassium was 3.3 mEq. per liter. Hemoglobin was 13.8 Gm. per 100 ml., with hematocrit 37 per cent and white blood count 7,200 per cubic millimeter, with 54 neutrophils, 5 eosinophils, 1 basophil, 33 lymphocytes and 7 monocytes.

She continued to do well and was afebrile throughout the remainder of her hospitalization. Intravenous fluids and oxygen were discontinued in the evening of the first posttransfusion day. She was discharged in good condition on the sixth posttransfusion day. Complete blood count at that time revealed hemoglobin of 14.2 Gm. per 100 ml., hematocrit 38 per cent, and white blood count 6,700 per cubic millimeter, with a normal differential count.

Follow-up Observations.—The patient was seen one week after discharge. There were no complaints and physical examination was normal. Her parents reported that her behavior was perfectly normal.

DISCUSSION

The poison in this case was Germtrol, a commercially available household disinfectant and cleaner. The toxic ingredient in Germtrol is pine oil, which comprises 49 per cent of the composition of the product. Pine oil is an oil obtained by steam distillation of the oleoresin from certain species of the

pine tree family. It is a mixture of terpene alcohols, chiefly alpha-terpineol, plus terpene hydrocarbons, borneol, and terpene ethers. It is used in the manufacture of terpin hydrate and other terpin products and as a solvent, disinfectant, and deodorant. Toxic symptoms may be produced by ingestion of small amounts of this complex mixture of terpene alcohols. It is irritating to the eyes and mucous membranes and often produces hemorrhagic gastritis when introduced into the stomach. Systemic effects include generalized weakness, decreased body temperature, central nervous system depression, and respiratory failure. It is readily absorbed from the gastrointestinal tract. Because of its chemical similarity to turpentine, treatment is the same as that recommended for turpentine poisoning.[18]

Although there have been no reports of dialysis or exchange transfusion used in this particular type of poisoning, we feel its use was justified because of the failure of supportive therapy to alter the progressive deterioration of the patient's condition. Death seemed imminent when exchange transfusion was decided upon. We cannot be certain what the eventual outcome would have been had an exchange not been done, but we feel that her recovery can be attributed to the use of exchange transfusion.

Because of the chemical relationship of pine oil and turpentine, the similarity of clinical symptoms, and the excellent response of this patient with pine oil poisoning to exchange transfusion, it is probable that severe cases of turpentine and other hydrocarbon poisoning would be benefited by exchange transfusion.

Both extracorporeal hemodialysis and exchange transfusion are extremely useful therapeutic measures in certain types of poisoning, and these procedures should be considered as methods of treatment in any patient with acute drug intoxication. Although widespread use of the artificial kidney is still limited, exchange transfusion is a procedure which, in experienced hands, can be carried out safely and with a minimum of special equipment.

SUMMARY

A case of acute poisoning caused by an enema containing pine oil is reported in a 4-year-old child. Exchange transfusion was successfully performed with rapid clinical improvement and eventual recovery. Exchange transfusion is recognized as the treatment of choice in selected types of acute poisonings, and its application in poisoning by hydrocarbons, such as turpentine and other volatile oils, warrants further study.

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"There is perhaps no subject which practitioners deem less worthy of their attention, than that of the nocturnal incontinence of urine amongst children . . . the majority of those who have written in relation to it have merely indulged in unique generalizations, from recollections only of what they have seen. . . .

". . . I was requested by some of the managers of the House of Refuge to suggest a cure of those of the children in that institution, who were in the frequent practice of wetting the bed. . . .

". . . I put them all on belladonna. . . . I also ordered that they should all have a dry supper of bread alone, as had been previously recommended, and the cold douche. Each boy was made to rise and urinate an hour after retiring for the night. Under this plan, the number of cases diminished with really astonishing rapidity. . . ."

Nocturnal Incontinence of Urine in Children, by Dr. Addinell Hewson. From the Transactions of the College of Physicians of Philadelphia, June 2, 1858.

AMEBIC ABSCESS OF THE LIVER IN A SIX-MONTH-OLD INFANT

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In 1943 Ochsner and De Bakey[1] reported 181 cases of amebic abscess of the liver and included an extensive review of the world literature on that subject. They indicated the rarity of amebic hepatic abscess in children, noting, however, that it has been reported in infants. They referred to 3 cases—in a 1-year-old child, reported in 1824, in an 11-month-old infant, reported in 1911, and in an 8-month-old, reported in 1930. In 1951 DeBakey and Ochsner[2] added 82 cases to their series and brought up to date the earlier review of the literature. The 1951 article made reference to 3 additional infants whose exact ages were not given. All 6 of these cases of amebic abscess of the liver in infants had first been reported in foreign medical journals. In 1955 Smith, Kidd, and Hashbarger[3] in this country reported a case in a 17-month-old white boy.

The case presented below is that of a 6-month-old Negro male. This is certainly one of the youngest patients with amebic hepatic abscess reported upon in medical literature, and it may well be the youngest.

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CASE REPORT

History.—A 6-month-old Negro male was admitted to the Pediatric Service of Confederate Memorial Medical Center with a history of diarrhea for 1 week and high fever for 4 days. The stools had contained blood for 4 days. There was no history of previous illness. There had been no known illness in the family. The patient had been referred to this hospital with a diagnosis of "possible viral meningitis."

Physical Examination.—On admission the patient was febrile and mildly dehydrated. He appeared to be ill but was in no acute distress. There was no bulging of the fontanel and no evidence of nuchal rigidity. The abdomen was soft and not tender. No masses were palpated. The remainder of the physical examination failed to reveal any further abnormality. The initial impression was that the infant had infectious diarrhea.

Hospital Course.—Early treatment consisted of an electrolyte solution and 5 per cent dextrose solution administered orally, Chloromycetin Palmatate, Kalpec, and measures to control fever. During the first week the patient had daily temperature spikes to 102.0 to 104.0° F., rectally. The diarrhea became intermittently better, then worse; the diet was adapted to the stage of the diarrhea. Daily physical examination failed to disclose any additional explanation for the fever. On the eighth hospital day a transfusion of 150 c.c. of whole blood was given. On the ninth hospital day

Fig. 1.

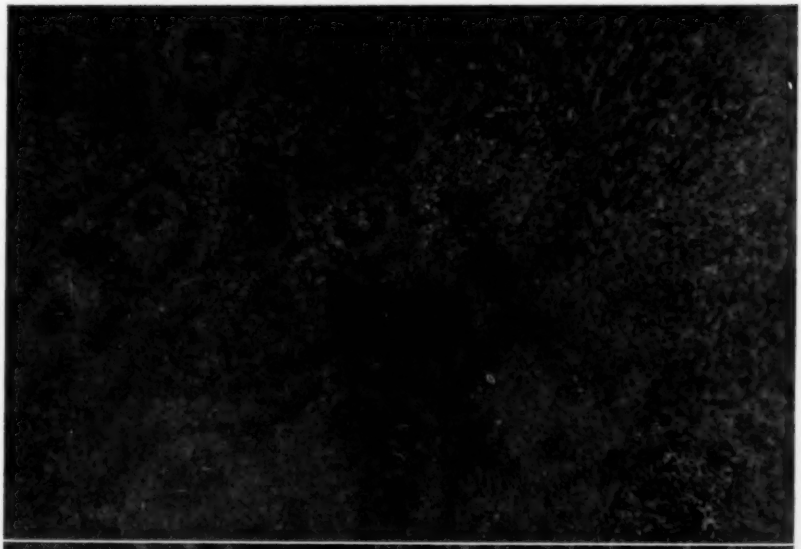

Fig. 2.

Fig. 1.—Amebic abscess of the liver.
Fig. 2.—Trophozoites in amebic abscess of the liver.

Fig. 3.

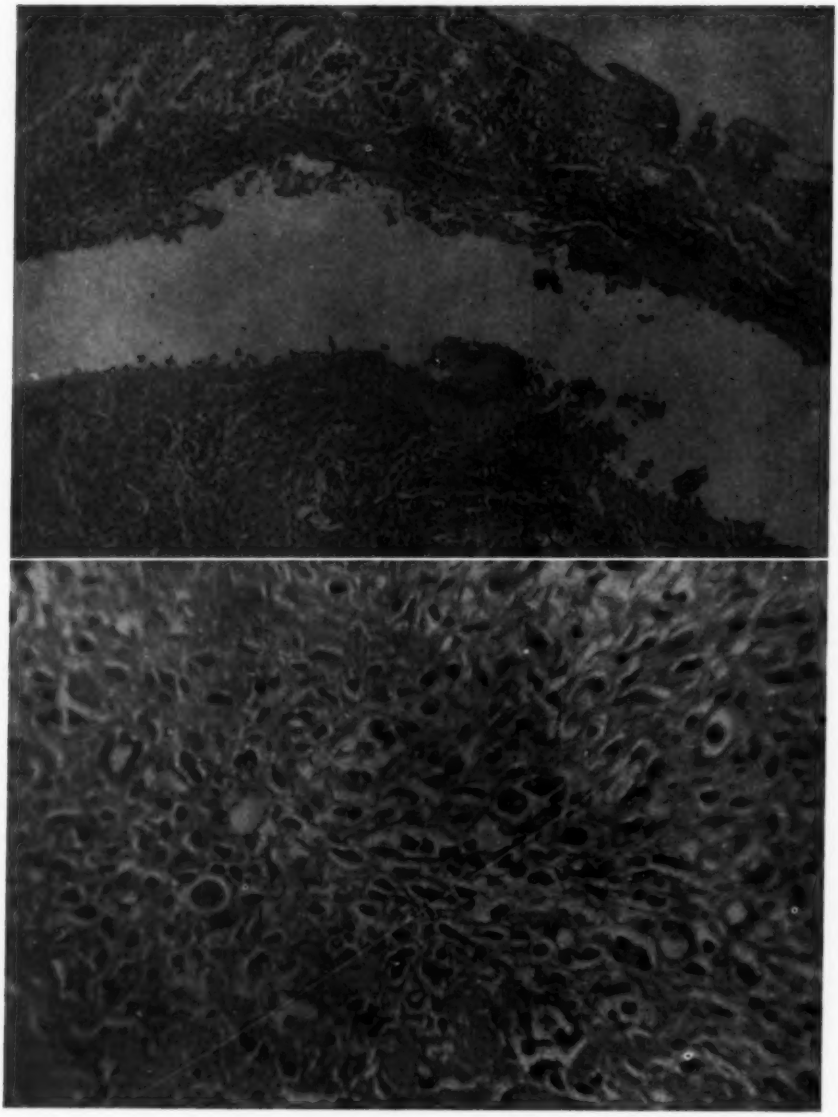

Fig. 4.

Fig. 3.—Amebic ulcer of the colon.
Fig. 4.—Trophozoites in the lymph channels of the wall of the colon.

the possibility of amebiasis was first suggested. Salmonellosis was also proposed as a diagnostic possibility. On the tenth hospital day a mass in the epigastrium was first noted. There was divided opinion as to the location of the mass, some observers believing it to be in the abdominal wall, while others held that it was in the abdominal cavity. Surgical consultation was obtained and exploration was not recommended. During this time the patient was having daily temperature spikes to 102.0° F., rectally. The diarrhea persisted and the general condition was unchanged. Treatment with antibioties and supportive therapy was continued. On the thirteenth hospital day one examiner suggested that the abdominal "mass" was actually the left lobe of the liver. Later that same day, after receiving a cleansing enema, the patient took a dramatic turn for the worse. The abdomen became markedly distended, two generalized convulsions occurred, and the patient became dyspneic, and vomited a dark brown liquid. In spite of intensive supportive therapy he died that evening.

Laboratory Data.—All urinalyses were normal. Stool cultures were negative for pathogens. Stool examinations for ova, cysts, and parasites were negative. Sickle cell preparation was negative. Spinal fluid was initially bloody but several days later was normal. One blood culture showed no growth after 10 days and another grew a Micrococcus, thought to be a contaminant. Hemoglobin ranged from 7.2 to 10.4 Gm. and leukocyte counts ranged from 7,100 to 19,300. All of the differential counts showed a shift to the left. Skin tests for tuberculosis and histoplasmosis were negative.

X-ray Findings.—The chest on the first hospital day was normal. The abdomen on the fifth hospital day was normal.

A barium enema on the tenth hospital day showed "diffuse narrowing of the colon distal to the splenic flexure and including the sigmoid and the rectum, with polypoid elevations of the mucosa." Polyposis with inflammation or primary inflammation with pseudopolypoid elevations was suggested.

On the thirteenth hospital day an x-ray of the abdomen showed gaseous distention of the proximal colon and the terminal ileum.

Necropsy.—Significant findings at autopsy were limited to the liver, colon, and peritoneum. The liver was brownish purple with a slightly mottled appearance and weighed 300 grams. On the anterior surface of the left lobe, near the inferior edge, was a 3.5 cm. yellow nodule. Another smaller nodule was found in the dome of the right lobe. On section these nodules were found to be encapsulated and to contain several small cavities with rough, shaggy walls. They were filled with a thick yellow pus. Microscopic examination revealed the presence of trophozoites of *Endameba histolytica* in the walls of the nodules (Figs. 1 and 2).

The colon measured 56 cm. in length. The mucosa was interspersed with shallow ulcers which had slightly rough to shaggy bases. They measured 1 to 4 cm. in length and up to 2 cm. in width. None were seen in the cecum. Several similar ulcers, however, were found in the ascending and transverse colon, more in the descending colon, and the greatest number in the sigmoid colon and rectum. The rectum exhibited red, raised areas of granulation tissue between the ulcers producing a pseudopolypoid appearance. Some of the ulcers were sharply demarcated and extended almost completely through the wall of the colon. There was a perforation at the rectosigmoid junction which was approximately 1 cm. in diameter. Microscopic examination of sections from the colon revealed the presence of trophozoites of *Endameba histolytica* (Figs. 3 and 4).

The peritoneum in the area of the perforation showed evidence of peritonitis both grossly and microscopically.

SUMMARY

A case of amebic abscess of the liver in a 6-month-old Negro male is presented. The condition is rare in infants and we believe this child to be one of the youngest such patients on record.

The autopsy was performed by Dr. Allen N. Weaver. The photomicrographs were made by Mr. Gordon Maxey.

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"When the child was first admitted into the hospital, on November 27th, she was ordered to have a grain of iodide of potassium three times a day in three drachms of carraway water. On November 29th, the dose was increased to two grains; and on the 30th, as the child complained of pain in the head, and there was great heat of the head, accompanied by a pulse of 150, the iodide of potassium was omitted, and she was ordered to have her head shaved and ice applied. This treatment persevered with until December 18th, when the iodide of potassium was again ordered, and she continued taking it until she left the hospital."

"Treatment of Cerebral Disease with Amaurosis in a Child," by Fred B. Jessett, Hospital for Sick Children. From the British Medical Journal, June 11, 1859.

Clinical Pathological Conference

The Children's Medical Center
Boston, Mass.

Sidney Farber, M.D., *Editor*
John M. Craig, M.D., *Assistant Editor*

CASE 1.—This 7-year-9-month-old white boy was in good health until 2 weeks prior to admission, when he developed a mild upper respiratory infection. He was afebrile but because of coughing could not attend school. Three days prior to admission he noted numbness of his hand. The following day he complained of throbbing headache in the left temporal region, as well as tenderness in the ankles and soles of the feet, and a sore throat. The morning prior to admission he began to develop weakness and a nasal voice.

Physical examination at this time revealed tonsillitis for which Tetracycline was prescribed. That evening he developed marked drooling and dysphagia. On the morning of admission to the hospital the child was unable to talk, swallow or lift his head.

He was admitted to an outside hospital where he was found to have a fixed, dilated right pupil, pharyngeal weakness, and difficulty in walking. A lumbar puncture yielded fluid containing 2 polymorphonuclear cells per cubic millimeter, a protein level of 20, and a sugar level of 20 mg. per cent. The peripheral leukocyte count was 25,000 per cubic millimeter, with 80 per cent polymorphonuclear cells.

The review of the past history revealed that he had received poliomyelitis and diphtheria-pertussis-tetanus immunizations 3 times.

On entry to The Children's Hospital after being held briefly in the previous hospital, the vital signs were: temperature, 99.6° F.; blood pressure, 118 mm. Hg systolic and 60 mm. Hg diastolic; pulse, 104; and respirations, 17 per minute. The child was below the third percentile for height and weight. He was underdeveloped and poorly nourished but alert and cooperative. There was generalized weakness. Neither the ears nor nose showed evidence of inflammation. The tonsils were hypertrophied and the reddened pharynx contained a mucopurulent discharge. A few rhonci were heard in an otherwise negative chest examination. The abdomen was negative. The neurological examination revealed a dilated fixed right, and a constricted but light-reacting left pupil. The patient could see, and a funduscopic examination was negative, yet there

was bilateral failure of lateral deviation of the eyes and ptosis of the right eyelid. Sensation in the face was normal, yet a facial paralysis was present. The patient had no gag reflex and could not swallow; no movement of the uvula could be detected. There was weakness of the flexors and rotators of the head, hands, forearms, and abdominal muscles, and of the proximal lower limb muscles, in comparison to the distal. The deep tendon reflexes were absent in all extremities. The plantar reflexes were down. All modalities of sensation were normal.

The initial laboratory examination gave the following values: hemoglobin, 14.8 Gm. per cent; hematocrit, 44 per cent; leukocytes, 161,000 per cubic millimeter with a differential count of 86 per cent polymorphonuclear cells; 9 per cent lymphocytes; 1 per cent monocytes and 4 per cent basophils. The sedimentation rate was 45 mm. per hour. The lumbar puncture yielded fluid under a pressure of 150 mm. of water. It contained no cells, a protein level of 13, and sugar level of 68 mg. per cent. Blood serum values were: pH 7.5; carbon dioxide content, 24.6; sodium, 136; potassium, 3.9; and chlorides, 93 mEq. per liter. The serum albumin level was 4.1 and globulin 3.2 Gm. per cent.

The child had a rapid downhill course, requiring a tracheotomy shortly after admission. Four hours later his muscular weakness had progressed and involved the diaphragm and intercostal muscles, with a reduction in his vital capacity to 200 c.c. He was placed in a tank respirator and his condition appeared to stabilize, but 36 hours after admission he suddenly became extremely cyanotic and died.

DR. EDWARD P. RICHARDSON, JR.*—As one thinks about what could have led to this child's death, with a very rapidly progressive generalized weakness of virtually all the musculature, not very many possibilities come to mind. This was a symmetrical weakness of the body musculature, progressing rapidly to involve the respiratory muscles and unassociated with any objective sensory changes in examination. We do notice, however, that early in this illness he observed numbness in the hand; later he complained of tenderness in the feet and ankles, and examination showed total absence of the deep reflexes. The spinal fluid on two occasions showed normal findings, and, of importance, there were no cells. The normality of the protein is an interesting fact which does not, however, militate against the supposition I have that this was a case of acute polyneuritis of unknown cause. I use this term in preference to acute infectious or infective polyneuritis, because, so far, this illness has never been demonstrated as being due to direct infection with any organism.

Are there any other forms of neuromuscular disease that have to be considered seriously in differential diagnosis of this case? The history of a severe sore throat at the beginning of this illness with severe tonsillar infection might raise the question of diphtheria and, as you know, infection with diphtheria is associated with toxemia that can result in a severe acute affection of peripheral nerves. However, the history states that this child was immunized against diphtheria, so that the chances of that infection seem

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virtually zero; the clinical course is not that of diphtheritic neuritis in that the patient developed generalized weakness of cranial and somatic musculature in the early phases of the present throat infection, rather than 2 or more weeks later as would be consistent with the course diphtheria. The upper respiratory infection that he had 2 weeks before admission, cannot, I think, be considered to play any definite part.

Other forms of multiple neuropathy cannot be diagnosed in this case because of lack of any definite evidence as, for instance, of an intoxication of some sort. It has been pointed out to me by one of my associates that a very rapidly developing multiple neuropathy may be associated with botulinus toxin. We have no evidence, however, that this was the case here. In such cases weakness of phonation and ocular palsies are supposed to be first in appearance. We have no evidence that this condition could be playing any part and I think it may be safely eliminated.

The chronic forms of multiple neuropathy such as nutritional, toxic (as with arsenic), familial, or sporadic cases of chronic multiple neuritis don't have to be considered because of the extremely rapidly developing nature of this condition.

What about intrinsic disorders of muscle? For the reasons immediately given, a chronic myopathy does not have to be considered. The possibility that this could be an acute myopathy, related to a disorder of electrolytes for instance, I think can be safely excluded because we have no evidence that there was any imbalance of that kind. Furthermore, we have some suggestion that there was some sensory involvement in this case. (Also, he was able to move his feet and toes to some extent, and the weakness was described as more pronounced proximally than distally.) Intrinsic disease of muscle, by and large, does not abolish the deep reflexes until the late stages, but this loss is an early and almost constant sign of affection of the peripheral nerves.

Having eliminated a number of possible disorders of neuromuscular function I come again to the supposition mentioned earlier—that this is a case of acute polyneuritis. After the clinical findings are reviewed, it must be said that everything we have here is perfectly consistent with that disorder. The very acute fulminating beginning and the ascending nature of the paralysis are entirely typical; the bilateral facial paralysis is a very constant finding. On the whole, ocular palsies in this condition are a very rare finding. Dr. Frank Walsh[1] speaks of occasional cases in which the third, fourth, or sixth nerves may be involved in this disorder. He points out that pupillary abnormalities may be very unusual but may occasionally be encountered. I think the finding of a unilateral fixed pupil is a most unusual manifestation in the condition that I am choosing, but I don't think that it rules it out by any means. We find that the ocular palsies were asymmetrical, with a partial third nerve palsy on the right, as shown by the ptosis of the lid and the fixed, dilated pupil; the other ocular movements seemed not to be disordered except for the bilateral lateral gaze movements, which, of course, are innervated by the sixth cranial nerves. Thus the sixth nerve on both sides was affected, and

the function of the third nerve was normal on the left and only partially affected on the right.

The absence of any sensory changes on examination in this condition is the rule rather than the exception in the form of polyneuritis that I am postulating. In case after case, one finds primarily a motor paralysis with reflex loss but without sensory changes, although it is very common for the patient, in giving the history, to relate some sensory changes subjectively, such as prickling, tingling, pins and needles in the extremities, or possibly soreness or tenderness; deep pressure to the muscles may elicit tenderness.

As far as the spinal fluid is concerned, the early publication of the French authors Guillain and Barré,[2] who described this condition, pointed out the association of a spinal fluid formula consisting of absence of cells and elevation of protein. This so-called "albuminocytologic dissociation" has occupied the attention of medical observers ever since that time and is a consistent feature in cases of this sort. It should be emphasized that in the early stages and in acute cases, the spinal fluid may be absolutely normal, as it was in this case, and the elevation of protein may not be observed until a week or two after the onset of the illness. I think a word of caution may be in order at this point about cases of this type of acute, fairly symmetrical weakness of the limbs in a young person, particularly a young woman, in the absence of any very definite objective changes other than the weakness. Occasionally such patients are seen and if, in taking the history, somebody has the idea that the young girl may be upset by any events around her, it may be thought that this is hysteria. It should be emphasized, in this connection that the loss of reflexes may not occur until some hours or days after the onset of the illness. Similarly, there may be no abnormality in the spinal fluid, as in this case. It was our experience, unfortunately, a number of years ago to have a young girl admitted under similar circumstances; it was felt that the complaint was a hysterical manifestation. She was placed in a room and nobody paid much attention to her until perhaps 6 or 8 hours later. She was then in severe respiratory distress and had to be placed in the respirator, unfortunately with a fatal outcome.

I have not mentioned poliomyelitis or any affection of the spinal cord itself. I think poliomyelitis is beyond consideration because of the normal spinal fluid, and I cannot think of any other disorder (developing so rapidly) of anterior horn cells in the spinal cord itself that could give this picture. We have seen material from a case which may be an exception to this in which a rapidly developing symmetrical weakness in a young child was thought to be poliomyelitis with a normal spinal fluid. However, the findings in this case are so unexpected and so unusual that it cannot be used as an example of what to consider when confronted with this type of clinical problem.

Are there any other points that should be reviewed in thinking about this case? The child apparently seemed to do well in the respirator for 36 hours and then suddenly became cyanotic and died. I think we can only speculate, but acute tracheobronchial obstruction comes to mind—a condition which might, of course, terminate life before anything could

be done about it. Pulmonary embolism is one of the things that one has to think of with adult patients, but I don't think it is a very common complication in young children.

A word or two might be in order as to the concept of this disease, "acute polyneuritis of unknown cause." This is an acute inflammatory disorder of peripheral nerves and the portions of peripheral nerves that appear principally to be affected are the nerve roots within the subarachnoid space at the entry and exit zones of the dura mater. A rather acute case in an adult, recently examined by us pathologically, shows us that the affection may be virtually limited to the anterior roots, with little or no affection of the spinal ganglia and no observable changes in the more distal peripheral nerves. In other cases one is likely to find spotty changes up and down the peripheral nerves, including the anterior and posterior roots and ganglia. The lesions consist essentially of small inflammatory infiltrates, combining lymphocytes, chiefly, with possibly a few plasma cells, and focal destruction of nerve fibers in association with these infiltrates, which tend to be perivascular. One may find destruction of the myelin alone, but in severe cases the myelin and axis cylinders both disintegrate and if the condition is severe and prolonged, one may find that the entire nerve becomes degenerated because of Wallerian degeneration. Some who have studied this condition have called attention to lesions in the central nervous system; these have been inconstant and in our own experience have been the exception rather than the rule. A recent survey of this illness occurring in young children is that of Weisse and Krücke[3] in Germany, who, in 3 fatal cases, point out small perivascular lymphocytic infiltrations with circumscribed white matter degeneration around small venules scattered here and there in the nervous system, together with the typical findings in the nerve roots. The presence of inflammatory infiltrates in the nerves of this type, unassociated with any demonstrable abnormality of the vessels themselves, and the distribution mentioned, serves to single out these cases from a pathologic standpoint, and although diphtheritic polyneuritis may have a similar distribution in the peripheral nerves, no significant inflammatory infiltrates seem to be present. The presence of inflammation in these cases is variable, but when marked there may be a pleocytosis in the spinal fluid of 5 to 10 lymphocytes. It seems very likely that the inflammatory infiltrates of the peripheral nerves at the level of the roots in the subarachnoid space account for the elevation of protein in the cerebrospinal fluid in such instances. The more distally placed peripheral neuropathies, such as those of nutritional or toxic origin, are not accompanied by an elevation of protein in the cerebrospinal fluid.

DR. FARBER.—Thank you Dr. Richardson.

DR. RANDOLPH K. BYERS.—There used to be a pretty certain clinical feeling that if the child with peripheral neuritis had dilated and fixed pupils or difficulties with accommodation, his neuritis was probably diphtheritic in origin, but it is quite evident that this child did not have diphtheria. It is an unusual finding in

cases of polyneuritis in children. I felt that this child was getting along fairly well after he was placed in the respirator, and I was astonished when I was told that he had died. I didn't know what the cause of death could be. It didn't seem to me, as I saw him shortly before he died, that there were any great changes in pulse rate or blood pressure which might suggest anoxia.

DR. CRAIG.—What is the mortality in such cases?

DR. BYERS.—Well, I think our experience here is quite different from the experience in most adult hospitals. These children do die. They may die in 2 ways: as this child did as the result of a rather acute rapid course of a few days' duration, or after a chronic relapsing course. There was one child on whom we did not get permission for a postmortem examination, but on whom I was never able to make any other diagnosis. This child pursued a relapsing course for about 2½ years with remissions and relapses and with no clear-cut evidences of central nervous system involvement. Her relapses were acute and sometimes accompanied by increases in the spinal fluid protein. I would say that our mortality rate, on the whole, is not more than 5 per cent. Recovery, when it occurs, is said to be complete. I don't know how you can predict weakness over a long period from the physical state during the acute attack of such an illness, but most of these patients are effective people. I think few of them are very good athletes.

DR. CRAIG.—What about acute porphyria, Dr. Richardson?

DR. RICHARDSON.—I wondered about that and since nothing was said about porphyrin being demonstrated in the urine I rejected the possibility. We don't have a history of a crisis of abdominal pain in this case and beyond having mentioned it, which probably I should have done, I don't think we can make that diagnosis here.

DR. CRAIG.—You base that on the absence of previous history and the absence of abdominal pain?

DR. RICHARDSON.—Yes, there is no history of a recurrent illness, nor is there any family history suggestive of this.

DR. BYERS.—Have patients with congenital porphyria been reported as young as this?

DR. RICHARDSON.—I wouldn't be thinking of it particularly at this age, though a few children have been recognized as having the disease.

A VISITOR.—What about acute Landry's paralysis?

DR. RICHARDSON.—In essence, as I understand it, without having read the original description, with Landry's paralysis one is dealing with an acute and rapidly ascending symmetrical weakness of the limbs. Landry had no way of making an adequate pathological examination of any of his cases. Dr. Madelaine Brown,[4] who reviewed that evidence at one time, thought that he might have been describing a severe nutritional neuropathy. Of the possible causes that produce a Landry paralysis syndrome, poliomyelitis or the acute polyneuritis discussed here should be mentioned.

DR. JOHN F. CRIGLER.—How frequent is the occurrence of severe tonsillitis in these patients with acute polyneuritis?

DR. RICHARDSON.—As far as the tonsillitis is concerned it has been pointed out that these cases may frequently be associated, at the onset, with the presence of a rather banal infection which need not be as severe as in this instance. The fact that the child had severe tonsillitis at the onset is interesting. I don't think it can be correlated in any very useful way at the moment. The present concept of this disorder, which I perhaps should have spoken of earlier, is that it may well represent a hypersensitivity phenomenon rather than any direct infection. A good reason for so thinking is based upon the work of Waksman and Adams[5] at our hospital, who have succeeded in producing what they have called "experimental allergic neuritis" in animals by injecting peripheral nerve tissue as an antigen. The lesions so produced and the cerebrospinal fluid changes show a striking resemblance to the findings in the human disease under discussion. These findings suggest that a similar mechanism may occur in cases in humans although the chain of events leading up to this is, of course, not understood.

DR. LOUIS K. DIAMOND.—What about therapy?

DR. RICHARDSON.—The efficacy of therapy with steroids has not been settled. Our own experience at the Massachusetts General Hospital has not been particularly favorable. We have had some cases that have terminated in death, unfortunately, despite steroid therapy. It has been reported as beneficial in occasional cases, but then some of these patients do extremely well without treatment and will recover rather rapidly; in others, it is a prolonged disease, dragging out over weeks and months. We ordinarily think of the prognosis of this illness as being good. If a patient can be carried through the terrible respiratory complications he should be able to live.

DR. DIAMOND.—I want to ask Dr. Byers how often he sees patients like this, whose protein level is not elevated and whose onset is more gradual than this?

DR. BYERS.—I think most of them do have elevated spinal fluid proteins. In Haymaker's article[6] a number of spinal fluid protein observations in proved cases were recorded; some had perfectly normal spinal fluid proteins throughout, with a flat course of several days; others had spinal fluid proteins that rose rapidly, and yet others had high spinal fluid proteins at the beginning that fell to normal while the sickness progressed. I don't believe that the spinal fluid protein is of any great help except when it is increased, without an accompanying increase in cells. A low spinal fluid protein does not exclude the disease.

DR. JONATHAN COHEN.—I would like to ask Dr. Richardson what he thinks the cause of death was? In polio patients with an equivalent amount of paralysis we wouldn't expect the patient to die in a respirator if the proper airway was maintained and the respirator was adequately ventilating his lungs.

DR. RICHARDSON.—My thought, Dr. Cohen, was that this was an accident of some kind. Possibly the patient did have tracheobronchial obstruction and died before anything could be done about it. I would agree with you that barring such accidents the course

should have been a reasonably favorable one. Dr. Byers pointed out that the patient's status gave no real cause for concern, even though he was in the respirator.

DR. FARBER.—What was the house diagnosis?

DR. SHERWIN V. KEVY.—The house diagnosis at the time the patient was admitted was the same as Dr. Richardson's today. The house staff this year also agreed with him and included the same differential diagnosis, except that in many instances they did mention poliomyelitis, relying on our experience in 1955, when we had about 6 or 7 children who had, on admission, normal spinal fluids, both proteins and cells, with later proved poliomyelitis. As far as the cause of death is concerned, we saw a lot of patients here in 1955 who died exactly as this patient did, with no evidence of acute respiratory obstruction; all of these had bulbar polio.

DR. JOHN F. CRIGLER.—Dr. Kevy, can you document the pulse and blood pressure in this patient in the hour immediately prior to death? Often poliomyelitis patients get sharp rises for a few hours before death occurs.

DR. KEVY.—This was unlike the polio patients who had a rising pulse and blood pressure. Up until minutes before his death the blood pressure was stabilized at 130/80, and the pulse remained steady.

DR. FARBER.—Now we will ask Dr. Betty Banker to describe the postmortem findings.

DR. BETTY Q. BANKER.—On gross examination the lungs showed scattered focal areas of atelectasis. The major bronchi were described as being filled with a combination of material which appeared to be blood and gastric contents. This was thought to represent a terminal aspiration, with some hemorrhage from the tracheotomy site. On microscopic examination many of the alveoli contained a proteinaceous edema fluid, and some areas appeared moderately atelectatic. A slight focal infiltrate of polymorphonuclear neutrophils was present and this was seen mostly around bronchi, so that the interpretation was of terminal aspiration, a pulmonary edema, mild atelectasis, and an early bronchopneumonia. The brain was swollen, weighing 1,384 grams, which is approximately 100 grams overweight for the size of this child. On examination of the external configurations of the brain, there were found tonsillar coning and a very slight uncal herniation bilaterally. Otherwise, the brain stem, cerebellum, spinal cord, peripheral nerves, nerve roots, and muscle appeared quite normal. On microscopic examination, while the cerebral hemispheres were normal, as Dr. Richardson has postulated, there was a very mild early axonal reaction which appeared to be present in the fourth and sixth nerve nuclei. The Nissl substance was displaced peripherally and there were occasional eccentric nuclei. In the cranial, cervical, and lumbar cord nerve roots there was an infiltration of lymphocytes between nerve fibers (Fig. 1). These were not present in all areas since they were present in motor but not in sensory roots, and more proximally than distally in the root. Most of the cells were lymphocytes, but occasional plasma cells and histiocytes were present. They were unusually

prominent in the perivascular area in the roots. In the sensory ganglia of cranial nerves, particularly the trigeminal and facial nerve, and also in the cervical dorsal ganglia, similar collections of cells were present (Fig. 2). Yet, the ganglion cells themselves were quite normal, and the satellite cells surrounding the ganglion, the astrocytes, also were normal in number. With myelin stains one can occasionally see areas that appear as if the myelin were breaking up into ovoid and ellipsoid bodies. We are not completely sure that this represents early demyelination. These findings then, as Dr. Richardson has postulated, were those that one would expected to find in the root and in the ganglia in the condition that he has described as *acute idiopathic polyneuritis* or *acute polyneuritis* of unknown etiology, which is also called *acute infectious polyneuritis*, and by some people, Landry's disease or Guillain-Barré syndrome.

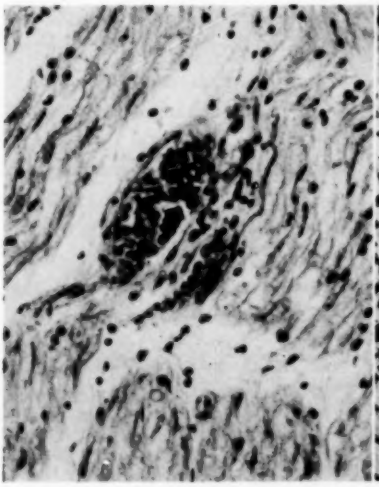

Fig. 1.

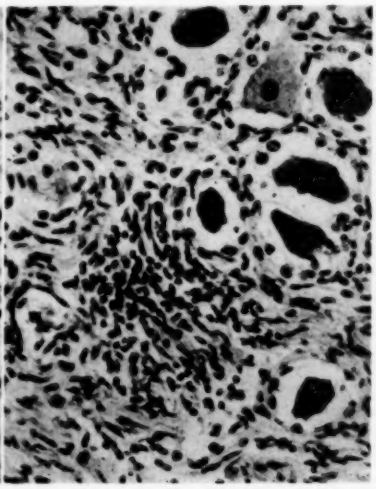

Fig. 2.

Fig. 1.—Photomicrograph. Anterior root spinal cord (14). Small round cell infiltration of the nerve is present. (Hematoxylin and eosin. ×400; reduced ⅓.)

Fig. 2.—Photomicrograph. Posterior root ganglion (L-4). An infiltration of the supporting elements by small dark inflammatory cells does not involve the ganglion elements. (Hematoxylin and eosin. ×450; reduced ⅓.)

Dr. Craig.—I wondered, Dr. Farber, if the possible viral etiology of this disease has been exploited sufficiently since postmortem material is usually obtained only late in the course of the disease. I am afraid that we were remiss in not giving some tissue to Dr. Kibrick for tissue culture studies. There has been a suggestive relationship of this disease to infectious mononucleosis. In the microscopic slides there is a very definite toxic reaction in the spleen, which suggests, by the reaction, that it is older than the pneumonia that the child had. I wonder, with modern isolation techniques, whether we may some day not find the agent. I find it difficult to believe the allergic concept since it would take a good deal of material injected into

an animal to produce such a reaction, and we do not have any such destruction of nerve tissue to start off this whole process.

DR. FARBER.—The histological picture is one just begging to be associated with a virus.

DR. SIDNEY KIBRICK.—I wonder if the situation here has the same etiological basis which is suggested in cerebellar ataxia. Large varieties of etiologies have been implicated and occasionally some viral agent is recovered in the stool. Now there has been some evidence of association of vestibular damage with ECHO 9 virus in the cases that occurred in the Milwaukee outbreak,[7] and in some cases with ECHO 9 virus isolations in this institution. We rarely get material on the acute cases; yet if the patient has been around several weeks and then dies, it is questionable whether you can recover a virus. The demonstration of an antibody rise in a response to an unknown antigen is impossible.

DR. FARBER.—Have you had a chance to study the spinal fluid of a child early in this disorder for viral agents?

DR. SIDNEY KIBRICK.—We have done spinal fluid examinations in other cases, not specifically with this disorder, but the situation may be a little like it in poliomyelitis, where there is just one case that I know of that seemed to be a clear-cut recovery of polio virus in the spinal fluid. Yet, in a number of related viral agents, *Coxsackie*, for instance, we have no difficulty in recovering virus in the spinal fluid.

DR. FARBER.—When you spoke of ataxia associated with a finding of virus in the stool, was there any proof of that association of stool virus with the ataxia?

DR. KIBRICK.—No, except that, again, in the cases of the Milwaukee outbreak this was found in a definite percentage of cases; the supposition is not based on finding one case with recovery of virus from the stool or spinal fluid, but it is based on some epidemiological considerations.

DR. FARBER.—But no reproduction of disorder of experimental animals in the monkey or any other animal?

DR. KIBRICK.—These patients did not die, and the changes associated with the ECHO 9 virus tend to be reversible. In regard to the diagnosis of polio in patients who have a normal lumbar spinal fluid, in such patients it has been found as high as 10 and 15 per cent. This reflects just the time the lumbar puncture is done.

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Comments on Current Literature

FAVISM

FAVISM is an acute illness characterized in its more severe form by hemolytic anemia, hemoglobinuria, and jaundice. Symptoms develop in susceptible individuals who come into contact with the broad bean, *Vicia fava,* either by inhaling the pollen of the flowering plant or by eating the mature bean. This bean, also known as the fava bean, or horse bean, is a common food in some parts of the world, especially in Southern Europe. Within recent years cultivation of the plant in the United States has been increasing; crops are harvested with regularity in western New York State, in New Jersey, in several New England states, and also in Illinois, Louisiana, Florida, Mississippi, and California. Reports from these areas cite the seasonal incidence of favism coincident with the flowering of the plant in spring or early summer and the use of the beans as food at the time of harvest. In some families the dried bean also has been used as a winter food. On drying, however, the bean loses much of its ability to evoke reaction in the human subject. Cases of severe asthma and hay fever have been observed in some farm workers or in others exposed to the pollen.

When the beans are eaten by susceptible children the manifestations may be delayed and the effects not immediately apparent. Usually, however, some evidence of the reaction can be noted within a day or two following exposure or ingestion. In one case with well-documented history reported by Lecks,[1] an Italian-American boy, 4 years of age, was brought to the outpatient department of the Buffalo Children's Hospital with the complaint of jaundice of 2 days' duration. Three days before admission the child had consumed 2 raw fava beans while the food was in preparation, and also had eaten a small portion of the cooked beans at the evening meal. Within 24 hours the mother noted the passage of dark urine, a manifestation which persisted. Jaundice, which was first evident in the eyes on the second morning, progressed to involve the skin of the entire body. Anorexia became marked, accompanied by occasional vomiting. Once, earlier, this same child had experienced severe urticaria following the administration of penicillin for otitis media. Other members of the family were in the habit of eating fava beans regularly with no ill effects. Inquiry into the family history, however, revealed that the child's paternal grandmother had suffered a number of attacks of jaundice after eating fava beans. On one occasion she had become ill and jaundiced after walking in a field of flowering fava plants. She stated also that one of her children, a daughter, had died at an early age after eating the beans as food.

The hospital course of the 4-year-old grandchild described was relatively uneventful. Except for the administration of ferrous sulfate by mouth, treatment was supportive; blood transfusion was not required. The clinical manifestations of favism subsided during the hospital stay of about 10 days; the anemia improved; the jaundice

cleared; the liver returned to normal size; and a precordial murmur which had been present on admission disappeared. The hematologic findings were within normal limits by the time of discharge and had remained so for a period of over 5 months at the time of this report. In another case from New York State, reported in detail by Larkin,[2] the untoward effects of fava beans as a food were not apparent for more than 3 weeks following ingestion. This child, a girl, one year of age, was referred to the hospital because of extreme pallor and evidence of hemolytic anemia. In this instance there was no evidence of liver enlargement and no jaundice.

Whatever the route of exposure, by inhalation of pollen or by ingestion of the raw or cooked bean, clinical manifestations vary widely in severity. In milder cases, especially in adults, the condition may be abortive, with headache, nausea, pallor, and transient pain in the legs, or merely headache and slight fever, with malaise for a period of a few hours, in which case the clinical course is suggestive of migraine. According to Larkin,[2] the degrees of severity in children include the following: a mild form consisting of moderate anemia, icterus, and slight hemoglobinuria; a grave form with weakness, prostration, marked pallor, moderate icterus, scant and bloody urine, diarrhea, and vomiting; and a fulminating form, seen largely in very young children, with intense anemia, hemoglobinuria, and shock. In this severe form, petechiae and ecchymoses may be present. Special forms have been described: cases with icterus as the only evidence and an urticarial form accompanied by intense itching. Blindness has been reported as a manifestation. In children, tachycardia is characteristic and a systolic murmur may be heard over the precordium. The liver may or may not be palpable; the spleen is often palpable and slightly tender.

Although favism has been recognized for many years, especially in the Mediterranean countries, where its pathogenesis has been studied intensively, the etiology of the condition has not been completely elucidated as yet. Cases were first reported in the United States about 1933. Early in the study of the disease, the possibility of a fava bean antigen and pollen allergens was suggested, with the implication that the clinical findings represent manifestations of a hypersensitivity state. That mild symptoms could be precipitated in some individuals by the intradermal injection of a minute amount of antigenic extract from the bean was also recognized very early, as was the tendency to familial susceptibility. The mechanism by which hemolysis of the erythrocytes is brought about is not understood thoroughly. Marcolongo and his co-workers[3] have offered autoimmunization and autosensitization as the most plausible explanation—similar to the phenomena associated with some other forms of acquired hemolytic anemia.

An interesting experimental approach to the problem of favism is presented in a recent issue of the *Journal of Allergy*. This report by Kantor and Arbesman[4] concerns "Serologic Studies on Favism." In this study, a hemagglutinating antibody against fava bean was found in immune antifava rabbit sera and, also, in the serum of a patient suffering from favism. The patient's serum sample was taken during the acute phase of the illness before blood transfusion or other therapy was instituted. Antifava rabbit serum was being investigated at the time and was obtained by subcutaneous inoculations of fava bean extract with an equal volume of Freund's adjuvant. Serum of normal rabbits served as control. A substance was present in the pretreatment serum of the patient with favism and in sera of rabbits immunized with fava bean extract which was capable of agglutinating human Group O, Rh-negative red blood cells previously treated with tannic acid and exposed to fava bean extract. The authors found that this

was a specific reaction which was minimal or which failed to occur at all with similar extract preparations from other types of beans, and which could be confirmed by inhibition studies. Normal persons and patients with favism who had been treated by blood transfusion and who recovered failed to show this type of serum antibody.

In summarizing their findings, Kantor and Arbesman[4] state that such serologic studies as these emphasize the immunologic etiology of favism. They point out, however, that the "role of this reaction in the pathogenesis of the disease remains to be elucidated by further studies with additional sera of patients prior to transfusions."

RUSSELL J. BLATTNER

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News and Notes

At the annual meeting of the **Chicago Pediatric Society** on May 19, 1959, the following officers were elected for the 1959-1960 year: president: Dr. Raymond F. Grissom; vice-president: Dr. Matthew M. Steiner; secretary: Dr. James A. Conner; treasurer: Dr. I. Pat Bronstein; editor: Dr. Howard S. Traisman; executive committee: Dr. Joseph Greengard, Dr. Ralph H. Kunstadter, Dr. Noel G. Shaw.

The **American Association for Cleft Palate Rehabilitation** will hold its 18th annual convention at the Brown Palace Hotel in Denver, Colo., on Thursday, Friday, and Saturday, May 12, 13, and 14, 1960.

The **American Psychosomatic Society** will hold its Seventeenth Annual Meeting at the Sheraton-Mt. Royal Hotel in Montreal, Canada, March 26 and 27, 1960.

Titles and abstracts, of 2 or 3 pages, in 9 copies, should be submitted for the Program Committee's consideration no later than December 1 to Eric D. Wittkower, M.D., 265 Nassau Road, Roosevelt, New York. Time allotted for presentation of each paper will be 10 or 20 minutes.

The **Second Annual Symposium in Cinefluorography** sponsored by the Department of Radiology, the University of Rochester School of Medicine and Dentistry, will be held Friday and Saturday, Nov. 13 and 14, 1959, at the University of Rochester Medical Center, Rochester 20, New York. The symposium will emphasize cardiovascular studies.

Submitted papers and inquiries should be directed to Dr. George H. Ramsey, Department of Radiology, Strong Memorial Hospital, Rochester 20, New York.

Dr. Horst Bickle of Marburg/Lahn, Germany, will give the **Third Annual Grover Powers Lecture** at the Yale School of Medicine, October 13 at 5:00 P.M.

Dr. Murray Davidson has been appointed Director of the Department of Pediatrics of The Bronx Hospital, 169th St. and Fulton Ave., it was announced by Abraham F. Wechsler, hospital president. He will start his new full-time post on Sept. 1. Dr. Davidson also was named Associate Clinical Professor of Pediatrics at Albert Einstein College of Medicine.

The Clinic of Child Development of the **Children's Hospital, Columbus, Ohio,** is offering training in developmental pediatrics and infant neurology on two levels. First, a fellowship for physicians, perferably pediatricians, recently completing their residencies. For those with additional qualifications, whether in pediatrics or in other fields, there is available a full-time staff appointment in the Department of Pediatrics of the Ohio State University College of Medicine.

For further information, write to the Clinic of Child Development, Children's Hospital, 561 South 17th St., Columbus 5, Ohio.

Officers and members elected to the **American Pediatric Society** at its annual meeting held at The Inn, Buck Hill Falls, Pennsylvania, May 7 and 8, 1959, are: President, Samuel Z. Levine; Vice-president, Hattie E. Alexander; Secretary-Treasurer, Aims C. McGuinness; Recorder (editor), Robert J. McKay; Member of Council (for 7 years), Herbert C. Miller, Jr.; and Members, Philip S. Barba, Philadelphia, Pa.; Randolph Batson, Nashville, Tenn.; Burtis B. Breese, Rochester, N. Y.; James DuShane,

Rochester, Minn.; Robert S. Ely, Little Rock, Ark.; Alfred L. Florman, New York, N. Y.; John Watson Gerrard, Saskatoon, Canada; Gordon E. Gibbs, Omaha, Neb.; David Goldring, St. Louis, Mo.; Robert H. High, Philadelphia, Pa.; Robert Kaye, Philadelphia, Pa.; Marion E. Leahey, Salt Lake City, Utah; Alexander Nadas, Boston, Mass.; Robert R. Struthers, Toronto, Canada; Clark D. West, Cincinnati, Ohio.

The 1960 meeting of the American Pediatric Society will be held Tuesday and Wednesday, May 5 and 6, at The New Ocean House, Swampscott, Mass. The Society for Pediatric Research will meet at the same place, May 3 and 4.

Books

The Onset of Stuttering, Research Findings and Implications. W. Johnson and Associates, Minneapolis, 1959, University of Minnesota Press, 518 pages. Price $5.00.

In a detailed presentation, the authors report on research in the pathology of stuttering conducted at the University of Iowa from 1934 to 1957. A portion of their research had been previously reported in other publications. The researchers were concerned with determining differences and similarities between nonstuttering and stuttering children. Analysis of the data, obtained by the case study method, suggests the differences between the two groups are few except in parental attitudes toward speech nonfluencies. It is postulated that misevaluation of normal nonfluencies as stuttering by auditors lay the groundwork for anxious, struggle reactions in the child's speech. Of particular interest are the authors' findings of only a few significant differences between parents of nonstuttering children and parents of stuttering children on the Minnesota Multiphasic Personality Inventory. This book is of interest because it represents the long-range work of outstanding speech pathologists and because the theory advanced has had pervasive influence in the field of communicative disorders.

Murray M. Halfond

Pathophysiology in Surgery. James Hardy, Baltimore, 1958, Williams & Wilkins Company, 704 pages. Price $19.00.

Applications of the basic medical sciences to the practice of surgery form the subject matter of the volume, *Pathophysiology in Surgery*, by James Hardy. Assimilation of things pertinent to the science of surgery from so many fields and the concentration of the material in a 600-page book are quite well done by Dr. Hardy. The advantage of a single authorship gives a continuity to the book lacking in other similar works. On the other hand, it is apparent in a few sections that the author does not write with the familiarity of one who has studied the subject matter of these sections at length in the laboratory. The author recognizes this in the preface but believes that one surgeon speaking to another can convey more understanding than a person working strictly in a preclinical medium could. Consequently, the book is primarily of interest to surgeons and is recommended for their attention.

William T. Newton

Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. Howard W. Jones, Jr., and William Wallace Scott, Baltimore, 1958, Williams & Wilkins Company, 456 pages. Price $16.00.

After reviewing this treatise, I am in complete agreement with the authors' statement in the preface, "this book is written about intersexuality for any student or physician who might be interested in the subject or have occasion to encounter such a patient." It is so compiled that one may obtain basic concepts and thus obtain the fundamental

background of these rather poorly understood conditions. In this respect, the first chapter, "Embryonic Sexual Differentiation," is well summarized and clearly presented.

This book brings one up to date on methods of diagnosis (including chromosomal sex differentiation), the endocrine and surgical aspects of treatment, the selection of sex, and, last but not least, the psychiatric and emotional (psychosexual) aspects in the management of patients with problems of sexual differentiation.

In the section concerning background of intersexuality, the following clinical conditions are discussed: The origin of the concept of hermaphroditism in Greco-Roman culture, embryonic sexual differentiation, the criteria of sex, and principles of treatment.

The clinical conditions are discussed in a clear, concise, and well-organized manner, with good coverage of the literature. The following outline is followed: (1) general considerations, (2) clinical characteristics, (3) laboratory findings, (4) pathological findings and changes, (5) pathogenesis, (6) treatment. There are well-documented case reports. Excellent illustrations, diagrams, and sketches are abundant. The following conditions are discussed: gonadal aplasia (dysplasia), Klinefelter's syndrome, hermaphroditismus verus, male hermaphroditism, female hermaphroditism due to congenital adrenal hyperplasia (adrenogenital syndrome), and female hermaphroditism without virilization. Conditions with genital anomalies which simulate hermaphroditism include: cryptorchidism, hypospadias, and anomalies of the vulva and vagina.

Discussions of gonadal tumors with sex reversal are classified as follows: masculinizing tumors of the ovary and endocrine tumors of the testis.

This book, when placed alongside the text, *Diagnosis and Treatment of Endocrine Disorders in Infancy and Adolescence*, by Lawson Wilkins, a well-recognized pediatric endocrinologist, also from Johns Hopkins University, will demonstrate considerable overlapping. In many respects, however, in the field of abnormalities of gonadal development, Dr. Wilkins' very excellent contribution will be complemented.

James N. Etteldorf

Inborn Errors of Metabolism. David Yi-Yung Hsia, Chicago, 1959, The Year Book Publishers, Inc., 358 pages. Price $9.50.

Books should always be reviewed with a clear knowledge of the aims of the author and of the audience for whom the book is intended. Dr. Hsia specifically states in the preface that "it is hoped that this volume will be helpful to the general practitioner and the house officer when they next come face to face with a patient who has a hereditary disease." Furthermore, in the foreword Dr. Gellis clearly states that "the present volume has been designed to review basic concepts and clinical aspects for the physician who is neither a geneticist nor enzyme chemist." This text has successfully accomplished both these objectives, and it should not be surprising that there is little information that is not covered in most standard pediatric texts.

Approximately 70 genetically determined disorders are covered. The clinical features, heredity, pathogenesis, diagnosis, and treatment are briefly considered for each disorder. A typical family pedigree chosen from the literature depicts the heredity of each condition and many charts are used to portray the "primary gene effect" as well as the site of metabolic block. The text is clear and concise and the format pleasing and attractive. The references are selected for their importance and are generally up to date.

A 55-page appendix of laboratory procedures is intended to "act as a readily available laboratory manual for their use in the detection of these conditions." The procedures described vary from a test for sickling to fluorescence microscopy, from the Lee-White clotting time to column chromatography for determination of amino acids, from the out-dated stool trypsin test to the elegant determination of galactose-1-PO_4 uridyl transferase activity. Many of the simple determinations are so universally available that there is little need to detail them and many of the more complex procedures are beyond the facilities and training available to most "general practitioners and house officers." The author admits that "a book of this nature must, of necessity, be incomplete, and many important things have had to be left out," but it seems to this reviewer that the appendix

could have been sacrificed and some of the more "important" subject matter could have been included.

There are some errors but they do not detract from the general usefulness of the book. For instance, on page 161, Sir William Osler is given credit for having first described a specific type of cretinism which results when there is failure of deiodination of iodotyrosines. It is obvious that Osler could not have known this type of goitrous cretinism from any other type in 1897. He did, however, reveal that 7 of 60 collected cases of sporadic cretinism were goitrous. On page 171 in a discussion of the salt-losing form of adrenal hyperplasia it is suggested that there may be a deficiency of "desoxycorticosterone" when aldosterone is obviously intended. On page 172 in the discussion of treatment of adrenal hyperplasia, "corticotropins" is erroneously used in place of the term, corticosteroids.

For the purpose intended, this book is adequate. However, the physician whose interest is more than a superficial one is referred to the rapidly accumulating literature on the subject.

Angelo M. DiGeorge

Correspondence

To the Editor:

I wish to correct a false statement that appeared in the JOURNAL and explain to its readers the background for the misstatement. An announcement was published (55:270, 1955), by request, of the formation of the Children's Exocrine Research Foundation to further research in cystic fibrosis. In a booklet sent us at that time, it was emphasized that *there would be no public appeal for funds*, but that the Foundation expected to obtain its funds from grants from other foundations and interested givers. It was further stated that the Foundation was *entirely expense-free* and that *100 per cent* of the money raised was to be used in research in this incurable disease. Three well-known pediatricians were named as the "Scientific Advisory Board"—names that indicated that the research funds would be wisely allocated and spent for worth-while projects.

What was of chief interest, and warranted publication of the announcement in the JOURNAL, was that this was not just another "Fund-for-a-Disease" organization, founded by individuals with an emotional urge, and that planned to put on a public campaign for funds for a specific disease, thus adding still another to compete for public support with the excessive number already in existence. Although there was a question in mind at that time as to the need for special funds for research in cystic fibrosis, in view of the rarity of the disease when compared with other equally fatal and crippling diseases, together with the splendid research in cystic fibrosis that had and was being done in children's hospitals in Boston and New York without the support of special funds, the uniqueness of the financial plans of the Foundation warranted publication. Certainly the gift of money for research by individuals who have for some reason a special interest in a particular disease is commendable and should be encouraged.

We were misled.

Nothing further was heard from or about the Foundation until an announcement in the St. Louis newspaper of May 29, 1959, that "a week-long fund drive by the St. Louis chapter of the National Cystic Fibrosis Research Foundation was started last night at a reception in the Junior League Tea Room. . . . A goal of $20,000 has been set. Volunteer workers will make *house-to-house calls* [italics ours] during the week. At the reception Dr. Wynne Sharples of Philadelphia, president of the national foundation and mother of two cystic fibrotic children, was honored."

Thus, the Foundation for research in cystic fibrosis, a lineal descendant of the "Exocrine Foundation," has made a volte-face and has turned out to be just another "Fund-for-a-Disease" organization competing for funds by doorbell solicitation. As is well documented, only a small part of the money collected by these organizations goes for research in the particular disease. Much of the promised "100 per cent" of the "expense-free" foundation's funds for research in cystic fibrosis seemingly will go down the drain of the cost of organization, fund raising, salaries, publicity, overhead, etc., as shown by the reports of similar "Fund-for-a-Disease" foundations and societies. We can well understand the personal interest of Dr. Sharples and her motivation, but this in itself is not justification for the cystic fibrosis foundation with all it entails and involves. In a booklet received since, it states that the local chapters may retain 15 per cent of the funds raised locally for operating expenses. In addition, the Fund has new offices, an executive secretary, and an administrative staff, although it states 85 per cent of the funds

raised—not 100 per cent as previously promised—will be spent for research. Further it announces an educational program. Either one or the other of us should go back and study arithmetic.

That cystic fibrosis is a disease warranting further research and study is beyond question. That a National Foundation with local chapters to conduct house-to-house solicitation for funds from the public for research in this disease is necessary or desirable is quite a different matter.

BORDEN S. VEEDER

To the Editor:

In the article by Leona Baumgartner and associates (J. PEDIAT. 54: 725, 1959), statistics were published which illustrated favorable effects of a premature program in New York City. This program provided for premature centers in several voluntary and municipal hospitals, enforced minimal standards and practices for premature care, and contributed full financial assistance to 83 per cent of families of premature infants cared for in approved premature centers in 1957.

Their statistics also disclosed that 30 per cent of all premature infants born in New York City in 1957 and 50 per cent of those born in hospitals having a premature center were non-white. Percentagewise, more non-white premature infants were born in the low-weight groups and their mortality exceeded that for white premature babies. These facts contribute further support to the role of maternal nutrition and socioeconomic conditions in the incidence of prematurity, birth in low-weight groups, and mortality.

Certain facts concerning the non-white population are indisputable. They have less income, more illness, a lower social and economic position, and inferior housing. They give birth to more premature infants, to a larger number in the low-weight groups, and sustain a greater loss of newborn infants.

Baumgartner and co-workers have demonstrated that a few more premature babies can survive with a vigorous public health program. This, however, does not alter the fact that the principal obstacles to reduction of fatalities are: (1) the great loss of infants born in the low-weight groups; (2) the short survival period of fatal cases; (3) the inadequacy of available means to sustain life and speed up the process of growth and development of most premature infants born in the low-weight groups to a level of maturity essential for life.

They have also contributed to a conviction, held by some, that the occurrence of premature birth is primarily a public health problem. Expanding their program to embrace prophylaxis of premature birth would be an important study. Such a program would include: (1) perinatal care and education of the mother beginning soon after conception; (2) provisions for adequate maternal nutrition; (3) severance from employment of working mothers for a period beginning shortly after conception until several months after delivery; (4) financial support for a period before and after delivery.

HARRY BLOCH, M.D.

Brooklyn, N. Y.

To the Editor:

I read Dr. Harry Bloch's letter with great interest. Economic status, maternal nutrition, maternal health, race, plurality of birth, mother's age, parity, and other related factors influence the incidence of prematurity.

In New York City in 1958, the incidence of prematurity on a city-wide basis was 9.1 per cent of the total births, with a marked variation by district from a low of 6.0 per cent in Bay Ridge, a relatively high socioeconomic district, to a high of 15.9 per cent in Central Harlem, a relatively low socioeconomic district, chiefly inhabited by non-whites.

The incidence of prematurity by ethnic groups in New York City this year is 7.9 per cent for whites and 15.0 per cent for non-whites. Some authorities believe that a difference in proportion of premature infants of whites and non-whites may be due in part to differences in nutrition, general health, and type of medical care received during pregnancy, rather than to racial factors. On the other hand, others believe that the gestation period for the non-white may be shorter than for the white and they suggest lowering the demarcating weight from 2,500 to 2,350 grams for prematurity

among non-whites, in order to approximate their stage of maturity to that of the white infants.

While the over-all premature mortality rate among the non-whites in our study is higher than among the whites, the mortality rate for non-white infants in each weight group is lower than among the white (see THE JOURNAL OF PEDIATRICS, June, 1959, Table 6, page 732), and we have therefore commented as to the relative maturity of the infants in each group when weight alone is used as the sole criterion.

Dr. Bloch is quite correct about the poor environmental and socioeconomic conditions of the non-white population in New York City. While our paper concerned itself chiefly with a description and analysis of the New York program for the *care* of premature infants, our ultimate goal is the total prevention of prematurity and we have been vitally concerned about it for many years.

While there are still many "undetermined" causes of prematurity, considerable knowledge already exists, which, if more widely applied, would help in making significant inroads in the prevention of prematurity.

Some of the preventive measures which can be immediately employed are:

1. Early and adequate prenatal supervision.

2. Improved facilities for prenatal supervision.

3. The same high quality of medical care which is available to individuals in the higher socioeconomic brackets made available to all.

4. Better facilities with better trained personnel.

5. Early detection of medical complications and their immediate treatment.

6. Education of the physician on the importance of noninterruption of pregnancies, except when it is absolutely indicated.

7. Education of the pregnant woman on the importance of prenatal care, diet, rest, and general health.

8. Establishment of perinatal mortality and morbidity committees at the hospital level to study carefully perinatal mortality and morbidity, with a view toward determining the causes and possible prevention, to identify the "premature susceptible" woman early, such as mothers with previous histories of premature births, and to take appropriate countermeasures.

9. Establishment of premature prevention committees at the medical society level, akin to the Accident Prevention Committees.

10. Intensification of research in all phases of prematurity, particularly those which will help us to learn more about the "undetermined" causes and their possible prevention.

To re-emphasize, the prevention of prematurity is a major public health problem, but it is not a medical problem alone. It requires the combined efforts of the medical profession and the health and welfare agencies.

HAROLD JACOBZINER, M.D.
Assistant Commissioner
Maternal and Child Health
The City of New York Department of Health

To the Editor:

The report on "Primary Fibrosarcoma of the Lung in a Young Child" which appears in the April, 1959, issue of THE JOURNAL OF PEDIATRICS has come to my attention.

Information now available requires that correction be made of the statement in the above-mentioned report to the effect that "this is the youngest case of this type of sarcoma of the lung ever recorded."

There is on record a case of an infant from which a fibrosarcoma of the lung was removed at the age of 2 days (Brit. J. Surg., September, 1958, p. 173). This patient was reported as being alive and making good progress 10 months after the operation.

This letter is not to be construed as being critical of the authors for not making a thorough search of the literature, for quite possibly the British report had not yet been distributed at the time the American report was submitted for publication. It is my desire solely to provide information that will contribute to the accuracy of the facts as already documented.

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Editor's Column

THE ROLE OF TUBERCULIN IN THE DETECTION OF TUBERCULOUS INFECTION

AMONG man's microbial enemies none has been more widespread throughout the world's population than the tubercle bacillus and none has been more effective in its destructive utilization of man as a host. Within the past half century man has gained significantly in his battle with this bacillus. It is not possible to assign credit precisely to any one of the various factors which have favored man in this competition. It is clear, however, that the individual whose general state of health is good is less apt to develop progressive disease than is the less healthy person. This feature is best illustrated in the prevalence of progressive tuberculosis in peoples of low economic status among whom malnutrition is common and among whom the manner of living is often notably unhygienic. The comparatively recent availability of specific antimicrobial agents, however, has provided the first effective means for a direct attack on the tubercle bacillus.

Essential to the control of tuberculosis is the detection of the infected person, followed by determination of the extent of his disease and of his infectiveness for others. No public health measure has been more effective in the control of tuberculosis than has the detection and subsequent isolation of "open carriers." Such detection has depended upon clinical appraisal, roentgenographic examinations, tuberculin testing, and identification of the tubercle bacillus. When the last is not possible, the differential diagnosis must be based upon probability, with various diseases taken into consideration, such as coccidioidomycosis, histoplasmosis, and other mycotic diseases, as well as a variety of bacterial ones which may simulate tuberculosis. In such instances the tuberculin test has played an important but variable role.

The story of tuberculin is an extremely interesting one. Introduced by Koch as a therapeutic agent in the latter part of the last century, it soon became apparent that such use was fraught with real danger and for practical purposes its use was abandoned. Subsequently Pottenger, Babcock, Hope Smith, and others have used it therapeutically, but the potential dangers from the infection of large amounts of tuberculin in the hypertensive person have served as a deterrent to its widespread use. Now that potent antimicrobial agents are available to lessen the likelihood of contiguous spread or hematogenous dissemination following its therapeutic administration, there may be only very limited uses for tuberculin therapeutically, such as for the rapid lysis of

lesions which can then be evacuated and removed surgically. Appropriate cases for such therapy are, however, extremely rare, and in most clinics tuberculin is not now used therapeutically.

Thus the clinical use of tuberculin is based mainly on its effectiveness as a skin testing agent for the identification of persons who have been infected with the tubercle bacillus. Pirquet deserves much of the credit for the establishment of tuberculin as a skin testing material. At this time (1909), the incidence of positive reactions in the population at large was so high that the use of the intradermal tuberculin test came to be discounted to a considerable extent as a diagnostic aid for the individual patient. Its effectiveness in identifying persons who had been infected with the tubercle bacillus, however, was generally accepted and it was and is widely employed for surveys of the incidence of tuberculous infections in population groups. As the incidence of tuberculous infections has decreased, the relative value of tuberculin used diagnostically in the individual patient has increased as it also has as a case-finding tool in population groups and within families.

A variety of investigative studies has contributed to the present status of the tuberculin test.

It was demonstrated early that the patient who had had a tuberculous infection as long as 6 to 10 weeks was most apt to have a skin reaction to tuberculin except as he was overwhelmingly ill with his tuberculous infection or except temporarily during an acute nontuberculous febrile illness. One of the shortcomings of tuberculin, however, was the variability in the potency of different batches of old tuberculin which was demonstrated in the twenties. Seibert's development of a more accurately standardizable tuberculin protein (PPD) for skin testing purposes has corrected this deficiency to a great extent and has directly and indirectly led to additional research.

The possibility that the intradermal injection of tuberculin might sensitize the host and thus be responsible itself for subsequent dermal reactions to tuberculin was a question which required an answer. It was demonstrated that although the available tuberculins were extremely weak antigens, within the range of the amounts used for skin testing there was no evidence of induced sensitization.

Quantitative differences in the degree of sensitivity in individuals with tuberculous infection were apparent practically from the start. As a result it became common practice to perform repeated tests with increasing amounts of tuberculin when the initial test was negative. It had been generally assumed that except as it was demonstrated that an individual failed to react to relatively large doses of tuberculin (O.T. up to 1.0 mg.; PPD up to 0.005 mg.) it could not be assumed that he was a nonreactor. The probability that many of the reactions to extremely large doses were nonspecific ones was clearly demonstrated by Furculow and his colleagues. It was found that practically all persons including newborn infants who failed to react to "average" testing doses did react to a much larger testing dose. Since the reactions which were elicited only with the extremely large doses of

tuberculin differed somewhat from the characteristic tuberculin reaction, it was concluded that they were not related to infection with the tubercle bacillus. On the basis of these observations and conclusions it was recommended that the top testing dose of PPD should be in the range of 0.002 mg.

In the course of the above investigations and also of several other ones, it was noted that a number of children who had calcified intrathoracic lesions failed to react to what were considered adequate testing amounts of tuberculin. The possibilities that this situation might reflect (1) loss of tuberculin allergy (reversal of reaction) or (2) residuals of infection with some agent other than the tubercle bacillus were considered. Although with Furculow, Palmer, and Hewell we embarked in the late thirties on a systematic testing program with antigens of microbial agents which possibly might be responsible for lesions resembling in one way or another those of tuberculosis, it was Charles E. Smith who suggested that histoplasmosis should be considered as an infection responsible for some of the calcified lesions which mimic those of tuberculosis. Shortly thereafter Christie and Palmer, separately, demonstrated the accuracy of this supposition, and it became evident that histoplasmosis was an extremely widespread infection occurring most often in a benign form in the midportion of the United States. The value of coordinated skin testing with tuberculin, coccidioidin, and histoplasmin is now well established.

The study reported in this issue on the interpretation of tuberculin sensitivity by Palmer and his co-workers provides another step and presumably an important one in the further clarification of tuberculin as a testing medium. To the deductions drawn in their paper, it seems meaningful to add the comments of one of our editorial reviewers:

"The proper interpretation of the tuberculin reaction is becoming increasingly important to the pediatrician. In children a positive tuberculin reaction is often the only evidence of tuberculous infection. In young children, it is considered serious enough to call for a prolonged period of antituberculosis therapy. Therefore, it becomes very important to define WHAT IS A POSITIVE TUBERCULIN REACTION.

"It must be emphasized that the interpretation of the tuberculin reaction is no longer a simple matter. We owe much to the authors of the paper in this issue whose intensive and extensive research on tuberculin sensitivity has demonstrated clearly that not all tuberculin reactions are due to tubercle bacilli. Reactions ranging from 6 to 12 mm. in size pose the greatest problem in interpretation because some of these small reactions are now known to be cross reactions from infections due to essentially nonpathogenic mycobacteria."

At the moment, the tuberculin test with all of its limitations provides the most effective means for the detection of tuberculous infection in the individual and in groups. The physician who accepts the continuous responsibility for the supervision of the health of a given child, and within varying limits of that of the child's family, must certify from time to

time that the family as an epidemiologic unit is free of tuberculous disease. He will do well to follow the advice of the committee on tuberculosis of the American Academy of Pediatrics as it is published in the Report of the Committee on the Control of Infectious Diseases, and perform tuberculin tests on each child at stated intervals and/or at such other times as there may be reason to suspect the presence of tuberculosis.

To the less exacting physician the apparent need for multiple skin tests with different testing mediums may be sufficient to lessen his use of the tuberculin test. The more careful physician will welcome any feature which adds to diagnostic precision. It is clear that there is need for further experience with antigens from bacteria such as the nonphotochromogenic mycobacteria which may produce cross reactions with the antigen of the tubercle bacillus. To this end it would seem wise to make available the "Battey" type antigen for skin testing purposes to a number of pediatric clinics for simultaneous use with PPD in order to extend the experience in individual children and especially in those with the smaller, questionably positive, reactions. Thus additional information would be provided concerning possible variations in the geographic distributions of these infectious agents whose antigens produce cross reactions with tuberculin, just as there are areal distributions of the mycotic agents of histoplasmosis and coccidioidomycosis.

W. E. N.